REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA 20-639
Sponsor: Zeneca Pharmaceuticals
Clock Date: July 29, 1996

Drug Name

Generic Name: Quetiapine fumarate
Trade Name: Seroquel

Drug Characterization

Pharmacologic Category: Serotonin and Dopamine Antagonist
Proposed Indication: Management of the Manifestations of Psychotic Disorders
NDA Classification: 1S
Dosage Forms: Oral tablets; 25, 100, and 200 mg

Reviewer Information

Clinical Reviewer: Andrew D. Mosholder, M.D.
Review Completion Date: June 13, 1997

1.0 Material Utilized in Review

1.1 Materials from NDA/IND

This NDA was submitted partly in hard copy and partly in electronic format. Case report forms were available only in electronic format, while certain study reports were available only in hard copy. Additionally, electronic datasets were provided for a variety of demographic, safety and efficacy parameters, both for individual studies and for selected pools of studies. Specific analyses or searches performed using these data sets are noted in this review.

The following documents were among those most frequently consulted, often in electronic format using the sponsor's CANDA, in preparing this review:

Integragted summary of efficacy
Integrated summary of safety
Study reports for trials 0006, 0008, 0012, 0013, and 0015
Four month safety update report 11/27/96
Literature summary (volume 283, hard copy only)
Report on thyroid data (4/14/97)

Information on Zeneca's commercial INDs for quetiapine

The following case report forms were examined: all deaths, and patients 0001/0014/1406, 0012/0091/9143, 0012/0019/1903, and 0012OLE/0002/0203.

1.2 Related Reviews, Consults, etc.

Consults have been received from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products, regarding the risk of cataracts with quetiapine treatment; from the Division of Gastrointestinal and Coagulation Drug Products, regarding white blood cell abnormalities with quetiapine treatment; and from the Division of Metabolic and Endocrine Drug Products, regarding the risk of hypothyroidism with quetiapine exposure.

1.3 Other Resources

Grateful acknowledgement is made to Dr.s Roberta Glass and Greg Burkhart, of the FDA's Division of Neuropharmacologic Drug Products, for their assistance with aspects of this review.

2.0 Background

2.1 Indication

There are currently over a dozen marketed antipsychotic compounds in the U.S. By convention, the efficacy of these drugs has been shown primarily in acutely psychotic schizophrenic patients, on the basis that drugs shown to be effective in such patients also are effective in other forms of psychosis such as mania, psychotic depression and the like. Only one marketed neuroleptic, clozapine, has been shown to be effective in patients refractory to other neuroleptic compounds. Use of clozapine is restricted to such refractory patients, however, because of the risk of agranulocytosis associated with clozapine therapy.

Traditional neuroleptics such as phenothiazines all block dopamine D2 receptors, and are associated with troublesome extrapyramidal side effects (EPS) and tardive dyskinesia. Recent interest in the field of antipsychotic drug development has focused on the so called serotonin-dopamine antagonists, sometimes designated SDA drugs. There is optimism in the field, as yet incomletely validated by clinical trial data, that such compounds will have certain desirable properties including lack of extrapyramidal sside effects, improved activity against the so called "negative" symptoms of schizophrenia, and freedom from tardive dyskinesia. The first such compound to be marketed domestically was risperidone; more recently, olanzepine was approved. Other serotonin dopamine antagonist drugs in late stages of development are ziprasidone and sertindole, the latter having significant cardiovascular toxicity due to prolongation of the QT interval. Quetiapine (Seroquel) is also a serotonin-dopamine antagonist, developed with the same rationale outlined above.

2.2 Important Information from Related INDs and NDAs and from Pharmacologically Related Agents

There is no specific information from related INDs or NDAs that is particularly relevant for the clinical review of quetiapine. There have been no INDs for the compound other than Zeneca's.

2.3 Administrative History

The original commercial IND for quetiapine.

Early in the development program, there was concern about preclinical findings of ophthalmalogical toxicity, and consequently ophthamalogic assessments were included in the safety monitoring of subjects. In October 1991, FDA permitted women of child bearing potential in clinical trials.

In February 1993, the sponsor and FDA held an End of Phase II meeting. In the latter part of 1993, Zeneca sought and obtained agency recommendations for a quetiapine study in treatment resistant schizophrenic patients (study 0031). In June 1995, Zeneca met with staff from FDA Biopharmaceutics to discuss aspects of the development program, and in the same month the sponsor and FDA held a pre-NDA meeting. At the pre-NDA meeting, it was agreed that efficacy analyses would include the Schedule for Assessment of Negative Symptoms (SANS) total score, and the standard 4 item psychosis cluster from the Brief Psychiatric Rating Scale (BPRS). Agreement was also reached on which clinical trials would be included in the primary integrated safety database.

FDA granted Zeneca a waiver for submission of hard copies of case report forms. In July 1995, Zeneca met with the agency to discuss the CANDA format.

2.4 Proposed Directions for Use

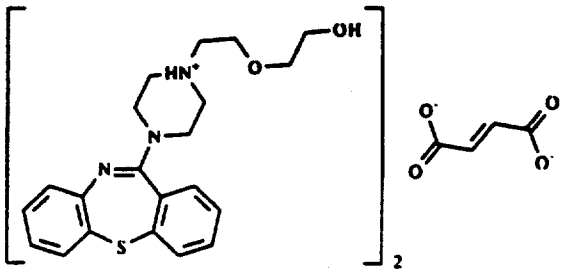
The draft labeling recommends the following: The starting dose should be 25 mg BID, with titration to a target dose of 300 mg/day over 4 days. The drug may be given on a TID schedule if desired. The maximum recommended dose is 800 mg/day; doses designated as effective in the clinical trials are as 150-750 mg/day, with maximal effect seen at 300 mg/day. The elderly, and patients with hepatic disease, should have slower titration and lower dosages. Some general guidance for re-initiation of treatment and for switching from other neuroleptics to Seroquel is provided.

2.5 Foreign Marketing

Quetiapine is not marketed anywhere in the world.

3.0 Chemistry

The chemical structure of quetiapine fumarate is shown below.



Quetiapine fumarate

I am not aware of any unresolved chemistry, manufacturing and controls issues that would preclude marketing approval.

4.0 Animal Pharmacology

Quetiapine is a serotonin and dopamine antagonist. The sponsor's table below displays the activity of the compound for various receptors, in terms of IC 50.

TABLE: Quetiapine affinity for multiple neurotransmitter receptors

	5-HT_{1A}	5-HT_2	D_1	D_2	H_1	α_1	α_1	Muscarinic	Benzodiazepine
IC_{50} (nM)	717	148	1268	329	30	94	271	> 10000	> 5000

From this, it will be seen that the compound has activity at a number of receptors, particularly 5HT2, D2, H1, and alpha-1.

Quetiapine is active in a number of animal models deemed predictive of antipsychotic effects, but shows less effects than standard neuroleptics in tests predictive for the development of EPS, such as catalepsy induction. The drug is proconvulsant in mice. In dogs, quetiepine did not appreciably alter the electrocardiogram. Prolactin elevations were observed, especially in rats.

Chronic toxicity studies were notable for development of cataracts in dogs, an effect the sponsor attributed to impairment of cholesterol biosynthesis. A number of thyroid gland abnormalities; e.g., thyroid follicular cell hypertrophy, were observed in various species. Hepatocyte hypertrophy was found in three species, attributed to hepatic enzyme induction. Carcinogenicity testing produced thyroid follicular cell adenomas in mice and mammary adenocarcinomas in rats.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program (Primary Source Data)

5.1.1 Study Type and Design/Patient Enumeration

Appendix table 5.1.1.1 displays the numbers of patients in the Integrated Primary Database for the quetiapine development program, as of the 3/1/96 cutoff date for the first NDA safety update. A total of 2,635 subjects and patients were exposed to quetiapine in the Phase I, II, or III clinical trials which Zeneca considered suitable for the primary integrated safety database. Of these, 343 subjects received quetiapine in Phase I trials and 2,387 patients received quetiapine in Phase II-III clinical trials; 95 of the latter group had prior exposure to quetiapine in Phase I studies.

Zeneca imposed a cutoff date of 6/1/95 for all safety data in the original NDA Integrated Primary Database, with a later cutoff date for serious adverse events. The 4 month safety update, however, provided comprehensive adverse event data through 3/1/96. Thus the primary integrated database available for this safety review included all adverse event data through 3/1/96.

Out of a total of 44 clinical trials, 5 phase I trials and 4 phase II-III trials were excluded from the primary integrated database, as will be described below.

Out of the 2387 quetiapine treated subjects in the Phase II-III primary database, 1711 were exposed in controlled clinical trials.

5.1.2 Demographics

Appendix Table 5.1.2.1 displays the demographic profile for the Phase I studies. As seen, Phase I studies involved primarily younger white males.

Appendix Table 5.1.2.2 shows the demographic characteristics for the Phase II-III integrated primary database. The subjects in the Phase II and III clinical trials were mostly white, predominantly male, and mostly younger than 40 years.

5.1.3 Extent of Exposure (dose/duration)

Appendix table 5.1.3.1 shows the duration of exposure by mean dose during Phase I studies, in terms of numbers of subjects exposed for a specific dose and duration. As expected for clinical pharmacology studies, the exposure was primarily at lower doses and at shorter durations.

Appendix table 5.1.3.2 dislays the same matix for the Phase II-III primary integrated database.

Of particular interest in the above table is the number of patients who received quetiapine in the recommended dose range. The draft labeling suggests a target dose of 300 mg/day, and it will be seen that there were a total of 1245 patients who received doses in the range of 150-450 mg. Wtih respect to duration of exposure, over 500 patients received the drug for approximately 6 months (i.e., 184 days) or more.

Appendix table 5.1.3.3 displays the overall exposure for quetiapine and control treatments in the primary integrated database, in terms of patient years (defined as the total days on therapy divided by 365).

5.2 Secondary Source Data

5.2.1 Non-IND and Excluded Studies

Zeneca chose to exclude certain clinical trials from the primary database, as discussed at the Pre-NDA meeting with the agency. Narrative summaries for deaths, withdrawals and serious adverse events were nonetheless provided for these studies in the Integrated Summary of Safety. The following is a list of the excluded studies. All the Japanese studies (those below whose study number starts with the letter H), phase I studies involving doses too small to be clinically relevant, and ongoing studies were excluded.

PHASE I STUDIES
SINGLE-DOSE TRIALS
204636/0001 (N = 9)
204636/0002 (N = 9)
H-15-11/12 (N = 17)
MULTIPLE-DOSE TRIALS
204636/0003 (N = 7)
H-15-13 (N = 8)

PHASE II-III STUDIES
5077IL/0031 (N = 18); STILL BLINDED/ONGOING
H-15-21 (N = 54) (OPEN LABEL)
H-15-22 (N = 165) (OPEN LABEL)
H-15-23 (N = 75) (OPEN LABEL)

Including these trials listed below, a total of 2,714 patients were known to have received quetiapine in the all completed and ongoing clinical studies, as of the 6/1/95 primary cutoff date for the ISS. The corresponding number of patients having received quetiapine in any integrated or nonintegrated trial as of the 3/1/96 cutoff date for the safety update was not specified.

Quetiapine is not marketed anywhere in the world. Zeneca has sponsored all clinical trials with quetiapine to date, and Zeneca has chosen not to make quetiapine available for compassionate use, so that the clinical data reported by Zeneca should represent all clinical experience with quetiapine.

5.2.2 Postmarketing Experience

Quetiapine is not marketed in any country.

5.2.3 Literature

As stated, all clinical trials with quetiapine have been conducted with Zeneca's sponsorship, and quetiapine has not been available for compassionate use; thus, no reports in the literature should involve additional clinical data beyond what Zeneca has already presented.

The sponsor submitted a preclinical and clinical bibliography, with reprints of the clinical references included (NDA volume 283). The cutoff date for the literature search was 4/16/96. The clinical bibliography comprised roughly 60 publications from U.S. and foreign journals. My own review of these publications did not disclose any new findings of significance. Additionally, Dr. Lisa Arvanitis, Zeneca's project physician for quetiapine, reported that she had reviewed the

literature and that it contained no unsuspected adverse safety findings.

5.3 Comment on Adequacy of Clinical Experience

In my judgement, the sponsor's clinical development program provides an adequate clinical data base for review of the NDA. The total numbers of patients exposed and the duration of exposure are comparable to the databases for antipsychotic compounds approved recently. Efficacy data is provided by more than one adequate and well controlled clinical study. No pediatric clinical data was provided; there was open label safety data provided for geriatric patients in study 0048.

5.4 Comment on Data Quality and Completeness

On balance, the data supplied in the NDA was judged to be of a sufficient quality to permit review. One exception to this involved individual patient data for some patients having serious adverse events; in a number of cases, the sponsor failed to provide sufficient clincal details or follow up information. Such cases will be described in the review of systems. Another data quality issue involved alllegations of misconduct on the part of one of the clinical investigators, Dr. Borison. Zeneca performed a reanalysis of their clinical data minus the data from Dr. Borison's site, and found that data from his site had little influence on the overall efficacy findings or the adverse event incidences. These re-analyses will be described.

6.0 Human Pharmacokinetic Considerations

Please refer to the biopharmaceutics review for complete details. Note that because healthy volunteers did not tolerate more than very low doses of the compound, much of the pharmacokinetic studies were performed with volunteer schizophrenic patients.

Quetiapine is rapidly and extensively absorbed after oral administration, and displays linear pharmacokinetics. The compound is primarily cleared by hepatic metabolism and is a cytochrome P450 3A4 substrate, with excretion mainly in urine and very little drug excreted unchanged. The major metabolites found in plasma are not very pharmacologically active. Terminal half life was determined to be roughly 7 hours; volume of distribution was 681 L. The sponsor states that plasma concentrations corresponding to clinical doses range from 200-3000 ng/ml. There is considerable interindividual variability in pharmacokinetics.

Quetiapine Cmax and AUC increased 25% and 15%, respectively, with feeding. The drug is moderately protein bound in plasma (83%).

With respect to special populations, mean clearance decreased up to 50% in elderly patients. Gender and race do not appear to have an effect on quetiapine pharmacokinetics. Severe renal insufficiency and hepatic disease were both observed to reduce clearance roughly 25%. Specific studies in special population subgroups are noted below.

Study 0016 was a pharmacokinetic study in schizophrenic men and women, treated with quetiapine titrated to 250 mg/d for 15 days. The sponsor reported no significant differences in pharmacokinetics or adverse events between males and females in this study; however, the sample was small (13 men and 15 women).

Study 0018 was a pharmacokinetic study in 8 nonpsychotic patients with cirrhosis and normal controls, administered a single 25 mg dose. Two of the eight patients had much lower clearance of quetiapine than observed in the normal control subjects. There were no unusual adverse

events among the patients with liver disease; however, this sample is very small.

Study 0019 was a pharmacokinetic study of a single 25 mg quetiapine dose administered to 8 renal patients and 8 normal controls. Zeneca concluded that there were no unique adverse events reported in renal patients given a single dose of quetiapine. Again, the sample size was very small.

Regarding drug interactions, the sponsor has concluded that quetiapine or its metabolites will not produce clinically meaningful inhibition of cytochromes P450 1A2, 2C9, 2C19, 2D6. or 3A4. Concomitant phenytoin resulted in a substantial increase in quetiapine clearance, possibly through induction of CYP 3A4; concomitant cimetidine had little effect on quetiapine pharmacokinetics. Coadministration of quetiapine did not effect the pharmacokinetics of antipyrine, lithium or lorazepam.

After the NDA was submitted, the sponsor submitted a brief report on the results of two other in vivo interaction studies, 0063 involving coadministration of fluoxetine and imipramine (n=26), and 0064 involving coadministration of haloperidol, risperidone and thioridazine (n=36). The sponsor concluded that quetiapine pharmacokinetics was not significantly affected by fluoxetine, imipramine, haloperidol or risperidone, while thioridazine appeared to induce metabolism of quetiapine with a corresponding reduction in AUC of 41%. The only adverse event of note during these studies was a conduction delay attributed to imipramine in one patient. These data have not yet been reviewed by the Biopharmaceutics reviewer.

7.0 Efficacy

7.1 Background

Zeneca has completed a total of 8 controlled clinical trials of quetiapine in the treatment of psychosis (please refer to the appendix table of all studies). Of these 8 studies, 4 can be considered capable by design of providing meaningful data on the efficacy of quetiapine in acutely ill schizophrenic patients. These studies provide the focus for the review of efficacy data; all were randomized, double blind, parallel group, multicenter 6 week trials, and all involved schizophrenic patients:

Study 0006, n= 109 total, comparing quetiapine 75-750 mg/day and placebo

Study 0008, n=266 total, comparing quetiapine $\leq$ 250 mg/day, quetiapine $\leq$ 750 mg/day, and placebo

Study 0013, n=361 total, a fixed dose study comparing quetiapine 75, 150, 300 mg, 600 mg, and 750 mg daily with haloperidol 12 mg/day and placebo

Study 0012, n=618 total, comparing quetiapine 225 mg BID, 150 mg TID, and 25 mg BID

Note that for studies 0006, 0008, and 0013, all quetiapine dosing was TID, while in study 0012 one group received TID dosing and the other two groups BID dosing.

The remaining 4 controlled trials will not be considered in detail in this review. One was a small pilot trial, Study 0004, which produced statistically significant results favoring quetiapine over placebo in the amelioration of psychotic symptoms, despite having an enrollment of only 12 subjects.

Study 0015, a relapse prevention trial one year in length, lacked a placebo control group and failed to show a difference in relapse rates among treatment groups. Thus it did not generate meaningful efficacy data.

The remaining 2 controlled trials (0007 and 0014) were 6 week long multicenter active controlled trials that failed to show a difference between quetiapine and the comparator drug (chlorpromazine in study 0007 and haloperidol in study 0014). In fact, the CGI results favored haloperidol over quetiapine in study 0014 (but there was no difference between treatments on the PANSS).

7.2 Review of individual studies

7.2.1 Study 0006

Investigator(s)/Location

The investigators and sites for this study are listed in Appendix table 7.2.1.1. This was a 12 site, U.S. study.

Study Plan

Objective(s)/Rationale

The objective of this study was to evaluate the safety and efficacy of quetiapine compared to placebo, in the treatment of hospitalized patients with acute exacerbations of chronic or subchronic schizophrenia.

Population

Patients were males and females incapable of becoming pregnant, aged 18-60 years. (The original protocol was amended to permit women of child bearing potential who were using contraception). Patients were required to be hospitalized and have a DSM III-R diagnosis of subchronic or chronic schizophrenia with acute exacerbation. Patients were required to be in general good physical health, with hypertension, substance abuse, other DSM Axis I disorders, mental retardation, epilepsy, suicidality, and allergies as reasons for exclusion. In addition, patients were required to have a minimum score of 45 on the Brief Psychiatric Rating Scale (BPRS), a score of at least 4 on the Clinical Global Impression (CGI) of severity, and a score of at least 4 on the core psychosis items of the BPRS (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content).

Design

Patients were to have discontinued all psychotropic medications at the beginning of the study, and were then to be treated with single blind placebo for at least 2 days. Patients who met the entry criteria at the end of the single blind placebo period were randomized to receive either quetiapine or placebo. Dosing was to start at 25 mg tid for the first one or two days. Beyond this, the protocol was not very specific regarding titration but did allow the investigator to increase the dose by 1 or 2 25 or 50 mg tablets up to 3 times per day. Dose increases up to 500 mg daily, and temporarily above 500 mg (to a maximum of 750 mg daily) for no more than 14 days, were permissable. Concomitant chloral hydrate, benztropine, and diphenhydramine were allowable. A subsequent amendment to the protocol permitted use of prn lorazepam.

Scheduled screening assessments consisted of history and physical examinations, ophthalmologic (slit lamp) examinations, vital signs, ECGs, clinical laboratories, and thyroid function tests. Weekly assessments included BPRS, CGI, Schedule for Negative Symptoms (SANS), Simpson rating scale for EPS, and Abnormal Involuntary Movement Scale (AIMS). Safety monitoring included vital signs, clinical laboratories, ECGs, and thyroid function tests. TreatTreatment was for 6 weeks, and a protocol amendment specified that patients were to remain hospitalized the entire time.

Analysis Plan

The primary outcome measure was defined a priori as the Brief Psychiatric Rating Scale (BPRS) total score, measured at endpoint (i.e., the last visit for which there is data). Analysis of covariance with baseline value, treatment and center, was designated in the protocol as the analytic method.

Study Conduct/Outcome

Patient Disposition

A total of 146 patients entered the screening phase of the trial, and of these, 109 completed the screening phase and were randomized. Of the 37 patients not randomized, the majority did not meet safety entry criteria, as shown in the table below, adapted from the sponsor's study report.

TABLE Screen failures - Trial 0006

Reasons for screen failure	n (%)
Intercurrent medical event	3
Refused to continue/lost to follow-up	1
Subject withdrew consent	4
Other	29
Clinically significant lab	6
Abnormal ophthalmologic exam	14
Hypertensive/hypertensive med	1
Clinically significant abnormal ECG	4
Alcohol/drug dependence	1
All criteria met	8
Total	37 (100)

The following table, reproduced from the sponsor's study report, displays the disposition of the patients randomized in the study. It will be seen that there were more discontinuations for treatment failure in the placebo group than the quetiapine group.

Study 0006: Numbers of patients and reasons for withdrawal

	Quetiapine (n = 54)	Placebo (n = 55)
Treatment failure	16	27
Protocol violation	1	0
Adverse clinical or laboratory experience	2	2
Withdrawal of consent	5	3
Other	2	1
Total number of patients withdrawn	26	33

Appendix table 7.1.2.3 presents the numbers of patients completing each week of the study, by treatment group. There were proportionately more patients in the placebo group dropping out during the later weeks of the study. At week 4, less than 70% of patients remained in either treatment group.

Demographics/Group Comparability

Appendix table 7.2.1.2 displays the demographic characteristics for subjects in this trial. The patients were primarily white males; the quetiapine and placebo groups were comparable with respect to demographic composition.

With respect to baseline comparability, there was not a statistically significant difference between groups for the total BPRS scores (quetiapine mean 55.8 versus placebo mean 54.1, p=0.19), but there was for the CGI severity scores (quetiapine mean 4.96 versus placebo mean 4.64,

p=0.03). No statistical testing was performed for baseline comparisons of SANS and BPRS psychosis cluster scores.

Dosing Information

Appendix table 7.2.1.4 presents the mean quetiapine dosage for patients remaining in the study at each week. The mean dose for completers remained around 400 mg/day for the final weeks of the study.

Concomitant Medications

The table below lists the use of selected concomitant medications by treatment group.

Selected concomitant medication use(adapted from electronic version of study report)

	Quetiapine n = 54	Placebo n = 55
Chloral Hydrate		
Number of patients	38	44
Benztropine mesylate		
Number of patients	5	6
Diphenhydramine HCl		
Number of patients	2	3
Lorazepam		
Number of patients	17	15

Overall the treatment groups were similar with respect to numbers of patients receiving these concomitant mediations.

Efficacy Results

Appendix tables present the efficiacy data for the important outcome measures (total BPRS score, CGI severity, BPRS psychosis cluster items, and SANS total score), by week, for each treatment group. Both the last observation carried forward (LOCF) analysis and the completers analysis are shown. In general, the quetiapine group was superior to the placebo group at several timepoints during the trial, but only by the last observation carried forward analysis. At the final week, the drug group was not superior to the placebo group at a 5% level of statistical significance on any measure, although several earlier weeks showed significance for the drug group on the BPRS total score, CGI severity, BPRS psychosis cluster, and SANS total score, especially in the LOCF analyses.

Miscellaneous Issues

Although there was imbalance at baseline with respect to CGI severity scores between the groups, analysis of covariance should have served to correct for this imbalance.

No plasma drug concnetrations were obtained during the study.

Because of allegations of misconduct at one site (Center 008, where Dr. Borison was the principal investigator), Zeneca provided a reanalysis of the efficacy data for the BPRS total socore and CGI severity score, omitting data from Center 008. This procedure had negligible impact on the results for these two variables, and there was generally no loss of statistical significance (in fact, some p-values were actually smaller without Center 008 data).

Conclusions

On balance, this study provides marginal support for antipsychotic efficacy of quetiapine, when titrated to a wide dose range. Strictly speaking, however, the data fall short of meeting the customary level of statistical proof, particlualy for the observed cases analyses.

7.2.2 Study 0008

Investigator(s)/Location

Appendix 7.2.2.1 lists the investigators and sites for this study, which was conducted in the U.S. and abroad.

Study Plan

Objective(s)/Rationale

This study was intended to determine the safety and efficacy of quetiapine, administered with low and high dosage regimens, versus placebo, for the treatment of hospitalized patients with an acute exacerbation of schizophrenia.

Population

Eligible subjects were male and female adults, aged 18-65 years; females of child bearing potential were permitted by a protocol amendment, provided they were using contraception. Patients had to meet DSM-III-R criteria for subchronic or chronic schizophrenia with acute exacerbation. Additionally, they were required to have a BPRS score of at least 27, a score of at least 4 on the CGI severity scale, and a score of at least 3 on 2 of the BPRS pschosis cluster items. The following were grounds for exclusion: use of antihypertensive medication, unstable medical conditions, substance abuse, suicidality, epilepsy, allergies, other DSMIII-R Axis I disorders. The protocol specified a target enrollment of 165 patients from the U.S. and overseas.

Design

This was a multicenter, double blind, randomized, parallel group, placebo controlled trial. Note that there were two separate protocols for this study, one for domestic sites and one for foreign sites. The two protocols were similar but not identical. Patients were required to be hospitalized for at least the first 4 weeks (later shortened to 3 weeks). There was no single blind placebo lead in period for this trial at foreign sites, although in the U.S. the study protocol specified a single blind placebo treatment of 2-14 days. Patients were to be randomized to either placebo, quetiapine 250 mg/d maximum or quetiapine 750 mg/d maximum. Medication was to be given QID at foreign sites and TID in the U.S., titrated according to clinical response, up to the randomly assigned maximum dose, for a duration of 6 weeks. The initial dose was to be 75 mg/d; beyond this, no specific titration schedule was set forth in the U.S. protocol. In the European protocol, the suggested maximum dosing schedule was as follows: Day 1, 75 mg; Day 2, 150 mg; Day 3, 250 mg; day 4, 350 mg; day 5, 500 mg; day 6, 600 mg; day 7, 750 mg. Patients were not to receive more than 500 mg daily for more than 2 weeks, however. Chloral hydrate, benztropine and diphenhydramine were allowable as concomitant psychotropic medications. Scheduled screening assessments included physical examinations, ophthalmologic examinations, ECGs, clinical laboratories, BPRS, CGI, Comprehensive Psychiatric Rating Scale

(CPRS), and PANSS. Assessments were scheduled weekly.

Analysis Plan

The primary outcome measures were defined as the BPRS and CGI scales, mean change from baseline.

Study Conduct/Outcome

Patient Disposition

In Europe, 117 patients entered the study and were randomized to double blind treatment. In the U.S., where patients first entered a single blind placebo period, 196 patients received single blind placebo, and a total of 169 were then randomized to double blind treatment. The majority of those not randomized failed to meet safety entry criteria. In addition, one patient in the U.K. apparently withdrew from the trial after receiving low dose quetiapine and re-enrolled in the high dose quetiapine group (with patient numbers UK-001/00019 and UK-001/00022, respectively). This patient was excluded from the analysis. Also, patient UK-001/00801 was excluded because of a diagnosis of schizophreniform disorder rather than schizophrenia: although this was permitted by a protocol amendment, this was the only non-schizophrenic patient in the study.

Overall, a total of 286 patients (117 European and 169 U.S.) were randomized to double blind treatment. Ninety six were assigned to high dose quetiapine, 94 to low dose quetiapine and 96 to placebo. This was considerably more than the planned number of patients (165 planned total), which Zeneca attributed to an increase in recruitment late in the trial. Apparently the sponsor believed that some of the European sites might not pass data quality audits, and to compensate the recruitment at other sites was boosted. As it turned out, no sites had to be excluded because of data quality concerns, and the end result was exess enrollment (see Zeneca's correspondence for details).

The table below displays the disposition of patients and the reasons for premature discontinuation by treatment group.

TABLE Numbers of patients and reasons for withdrawal, Study 0008 (adapted from sponsor's electronic version of study report)

	Quetiapine		Placebo
	High dose (n = 96)	Low dose (n = 94)	(n = 96)
Treatment failure	25	34	42
Protocol violation	1	1	0
Adverse clinical or laboratory experience	7	7	3
Death during randomised treatment	0	0	0
Withdrawal of consent	10	4	8
Intercurrent medical event	1	1	0
Other	4	7	4
Total number of patients withdrawn	48	54	57

Not surprisingly, the placebo group had the highest dropout rate for treatment failure, and in fact had the highest droupout rate overall by a slight margin.

Appendix table 7.2.2.2 shows the numbers of patients remaining in each treatment group by week.

Demographics/Group Comparability

The patients in this study were primarily male caucasians, with a mean age in the late thirties. Appendix table 7.2.2.1 shows the demographic characteristics by treatment group. There was no obvious imbalance between treatment groups with respect to demographic characteristics.

Regarding baseline comparability, the Kruskal Wallace test for a difference among the three groups was marginally significant (p=0.06) for baseline BPRS scores, with the high dose group having a mean score roughly 3 points higher than the placebo group, as seen in the appendix tables. Differences between treatment groups on the CGI severity and SANS were not as statistically significant.

Dosing Information

Appendix table 7.2.2.3 lists the mean daily dose for patients in both quetiapine groups completing each week of the study. After titration the low dose group generally had mean doses close to 250 mg/d, and the high dose group had mean doses aroung 500 mg/d. Thus, dosing was close to the maximum on average for the low dose but well below the maximum on average for the high dose group. This likely reflected the prohibition on dosing above 500 mg for more than 2 weeks.

Concomitant Medications

The study report provided information on concomitant medications for agitation, insomnia and EPS. Anti-EPS medications were administered to 7 of 96 (7%) high dose quetiapine patients, 3 of 94 (3%) low dose patients, and 10 of 96 (10%) placebo patients. Chloral hydrate was given to 51 of 96 high dose patients (53%), 49 of 94 (52%) low dose patients, and 49 of 96 (51%) placebo patients. Some type of benzodiazepine was administered to 36 of the 96 (38%) high dose patients, 48 of 94 (51%) low dose patients, and 38 of 96 (40%) placebo patients. Thus there was not a large imbalance with respect to use of concomitant medications in the three treatment

groups. The use of anti-EPS medication was actually highest in the placebo group.

Efficacy Results

Appendix tables display the results for the primary efficacy measures. On the BPRS total score, the high dose quetiapine group showed a statistically significant improvement relative to placebo with both the LOCF analysis and the observed cases analysis. This was not the case for the low dose group, however. The same pattern of results was obtained with the CGI severity scores, the BPRS psychosis cluster scores,and the SANS total scores (the latter administered only in the U.S.). The PANSS, on the other hand, was administered only in Europe, and the negative PANSS scale generally did not show statistical superiority for either active drug group over placebo; however, the sample size may have been inadequate for statistical power, since results were consistently numerically superior for the high dose group.

Miscellaneous Issues

It is not likely that the baseline imbalance with respect to BPRS scores biased the results in favor of the high dose group. Analysis of covariance should have accounted for this imbalance.

There was a substantial over enrollment of patients in this trial relative to the protocol specified target. However, this did not appear to be a result of an interim analysis suggesting a need for more patients to be enrolled, as the sponsor affirmed that no interim data analysis was performed. Furthermore, an analysis by the Biometrics reviewer, Dr. David Hoberman, showed that even if enrollment had been stopped after the first 165 patients, as originally planned, the results would still have shown superiority for quetiapine; please refer to Dr. Hoberman's review for details.

In the U.S. plasma concentration data was obtained. The median plasma concentration of quetiapine at week 6 was 42 ng/ml for the 250 mg dose group and 68 ng/ml for the 750 mg/d dose group. No statistical correlation between plasma concentration and improvement on efficacy measurements was found.

Conclusions

On balance, this study provides statistical evidence that quetiapine administered at a high dose (i.e., roughly 500 mg daily) is effective in the treatment of psychosis associated with schizophrenia. Improvement was found in both positive and negative symptomatology. Efficacy of the lower dose, roughly 250 mg on average, was not supported.

7.2.3 Study 0013

Investigator(s)/Location

The investigators and sites for study 0013 are listed in appendix 7.2.3. Sites were in the U.S. and Canada.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to determine the dose-response relationship for quetiapine in the treatment patients with acute exacerbation of schizophrenia.

Population

Targeted enrollment was a total of 350 patients (50 per treatment arm). Eligible patients were those aged 18 to 65 with chronic or subchronic DSM-IIIR schizophrenia, in acute exacerbation. Mental retardation, organic mental disorder, substance abuse, seizures, pregnancy, breast feeding, leukopenia, unstable medical illness, history of clozapine related agranulocytosis, or abnormal ECG were all grounds for exclusion. Patients were to have a minimum score of 27 on the BPRS, a minimum score of 4 on the CGI severity rating, and a minimum score of 3 on the four item psychosis cluster of the BPRS. Also, patients were not to have demonstrated a more than 20% improvement in the BPRS, or an improvement of more than 1 point on the CGI, during the one week screening period.

Design

Patients were to be hospitalized for at least the first 4 weeks of double blind treatment. The study began with a 3-7 day single blind placebo lead in period, after which patients were to be randomly assigned to one of the following seven double blind treatments: haloperidol 12 mg/d, placebo, quetiapine 75 mg/d, quetiapine 150 mg/d, quetiapine 300 mg/d, quetiaine 600 mg/d, quetiapine 750 mg/d. Dosing of study medication was to be TID, and the medication dose was to be titrated during the first 1-2 weeks of double blind treatment and remain constant during the final 4 weeks. The recommended titration schedule was as follows for the 750 mg dose: Day 1, 75 mg; day 2, 150 mg; day 3, 250 mg; day 4, 300 mg; day 5, 400 mg; day 6, 600 mg; day 7, 750 mg. Scheduled screening procedures included history and physical examination, BPRS, CGI, hematology laboratories, liver functon tests, thyroid function tests, pregnancy testing, ECGs, and prolactin levels. Baseline assessments were scheduled at the end of the single blind placebo wash out period, and patients were to be assessed weekly during double blind treatment. Efficacy measures included BPRS, CGI and SANS, and safety assessments included vital signs, clinical laboratories, and EPS rating scales. Chloral hydrate, lorazepam, and benztropine could be provided as needed, and medication for stable medical conditions was allowed. Open label treatment was permissable for patients who had completed at least 2 weeks of double blind treatment.

Analysis Plan

The BPRS total score and the CGI severity score, considered at endpoint, were the designated primary outcome measures. The primary method of analysis was designated as a dose-response model, rather than pairwise comparisons to placebo.

Study Conduct/Outcome

Patient Disposition

A total of 402 patients entered the single blind phase of the trial; 41 of these discontinued before randomization (chiefly because of withdrawal of consent). Thus, 361 patients were randomized to double blind treatment, with roughly 50 patients entering each of the 7 treatment arms. The percentage of patients completing each week of the study is shown in the appendix table by treatment group. Less than half the patients in the trial completed the study, although retention is some groups was higher than others.

The overall disposition of patients in each treatment group is shown in table 7.2.3.1 below.

TABLE 7.2.3.1 Numbers (%) of patients and reasons for withdrawal (adapted from the sponsor's electronic study report)

Treatment Group:	Quetiapine					Haloperidol	Placebo
	75 mg (n = 53)	150 mg (n = 48)	300 mg (n = 52)	600 mg (n = 51)	750 mg (n = 54)	(n = 52)	(n = 51)
Total number of patients withdrawn	36 (68)	27 (56)	28 (54)	24 (47)	28 (52)	34 (65)	35 (69)
Reason for withdrawal							
Lack of efficacy	27	23	22	16	19	17	30
Refusal to continue/ failed to return	8	4	5	7	6	13	3
Adverse experience/ intercurrent illness	0	0	0	0	1	4	2
Protocol noncompliance	1	0	1	1	2	0	0

In all treatment groups, discontinuations for lack of effect outnumbered discontinuations for adverse experiences.

The appendix table 7.2.3.2 displays the completion rate for each week of the study by treatment group.

Demographics/Group Comparability

Appendix table 7.2.3.1 shows the demographic characteristics of the patient population in this study. In all treatment groups, patients were chiefly white males; the mean age in all groups was in the late thirties. Paranoid schizophrenia was the most common diagnosis.

With respect to baseline comparability, Zeneca stated in the study report that there were no statistically significant differences at baseline between treatment groups, but I was unable to locate a supporting analysis in the study report.

Dosing Information

This was a fixed dose study.

Concomitant Medications

In the quetiapine groups, use of concomitant benztropine ranged from 8-12% of patients. The majority of patients in all groups received chloral hydrate, and roughly half of patients in most treatment groups received lorazepam. The table below displays the use of these three medications by treatment group.

TABLE 7.2.3.2 Selected concurrent medication use (adapted from sponsor's electronic study report)

Medication	Treatment group SEROQUEL 75 mg (n = 53)	150 mg (n = 48)	300 mg (n = 52)	600 mg (n = 51)	750 mg (n = 54)	Haloperidol (n = 52)	Placebo (n = 51)
Chloral hydrate							
Number of patients (%)	36 (68)	29 (60)	34 (65)	31 (61)	33 (61)	41 (79)	40 (78)
Lorazepam							
Number of patients (%)	33 (62)	23 (48)	26 (50)	22 (43)	26 (48)	32 (62)	25 (49)
Benztropine mesylate							
Number of patients (%)	6 (11)	5 (10)	4 (8)	6 (12)	6 (11)	25 (48)	7 (14)

Efficacy Results

Appendix tables show the results for the primary outcome measures. With respect to the BPRS total score, the CGI severity scores, and the BPRS psychosis cluster, efficacy results by LOCF showed statistically significant results relative to placebo for all doses except 75 mg/d. The findings on the observed cases analysis were not as robust, particularly towards the later weeks in the trial, but this is not unusual for antipsychotic clinical trials with large numbers of dropouts. The haloperidol 12 mg group showed statistical superiority on all three of the above measures as well, and generally performed better in the observed cases analysis than any of the quetiapine groups. Other than the observation that the lowest dose (75 mg/d) of quetiapine was the only dose which did not show an effect, there appeared to be little evidence for a dose response effect, as the size of the mean changes from baseline was fairly consistent across dose groups.

For negative symptoms, the quetiapine 300 mg and the haloperidol groups showed statistical superiority to placebo on both LOCF and OC analyses. The quetiapine 600 mg/d group also demonstrated some efficacy versus placebo, although not as consistently as the 300 mg and haloperidol groups.

Miscellaneous Issues

No statistical correlation was found for plasma drug concentration and outcome on efficacy measurements. Plasma drug concentrations for patients completing week 6 are shown below.

Table: Plasma drug concentraionts at week 6 by dose, study 0013:

DOSE (MG/D)	MEAN (SD) TROUGH QUETIAPINE CONCENTRATION (NG/ML)
75	14 (11)
150	28 (16)
300	44 (34)
600	91 (59)
750	94 (72)

Because of allegations of misconduct at Dr. Borison's center, Center 001, Zeneca reanalyzed the efficacy results minus data from Center 001 (submission of 9/24/96). The results for BPRS total score and CGI severity score changed only slightly when data from Center 001 was omitted, and statistical comparisons to placebo were essentially unchanged.

Conclusions

This trial provides statistical evidence that quetiapine is active in the treatment of psychotic schizophrenic patients, at doses of 150 mg/d and above. The 75 mg/d dose did not demonstrate efficacy, however. For the other quetiapine dose groups and the haloperidol active control, primary efficacy results were comparable, and no dose response relationship for doses above 75 mg/d was evident. There was evidence for reduction in negative symptoms, as measured by the SANS, for the haloperidol group and the quetiapine 300 mg group. The improvement seen for negative symptoms with haloperidol treatment is of interest, since many experts believe that traditional antipsychotic drugs are not as capable of ameliorating negative schizophrenic symptoms as are newer medications.

7.2.4 Study 0012

Investigator(s)/Location

A total of 89 centers in various foreign countries participated in this trial; no domestic sites participated. The investigators and sites for this study are listed in appendix 7.2.4. Note that Center 10 was omitted from the analysis after Zeneca learned that the investigator had allegedly committed fraud during a previous clinical investigation.

Study Plan

Objective(s)/Rationale

The purpose of this study was to compare the efficacy and safety of quetiapine administered 225 mg BID, 150 mg TID, and 25 mg BID, in the treatment of patients with an acute exacerbation of chronic or subchronic schizophrenia. The goal was to provide support for dosing quetiapine BID rather than TID, with the expectation that a BID dose regimen will improve compliance.

Population

Subjects were to be inpatients with an acute exacerbation of subchronic or chronic schizophrenia (as per DSM-III-R). The goal was to recruit 510 subjects. Adult males or females, aged 18-65, were eligible, but females were to have a negative pregnancy test if of child bearing age, and were not to be breast feeding. Subjects were to have a minimum CGI Severity score of 4, and a minimum BPRS total score of 27, with a score of at least 3 on two or more of the BPRS psychosis cluster items. Exclusion criteria encompassed substance abuse, organic mental disorder, mental retardation, previous exposure to quetiapine, history of clozapine related agranulocytosis, seizures, and presence of risk factors for blood borne infections such as HIV or hepatitis.

Design

The study design included three phases. The initial phase was a no medication washout period, followed by a 6 week, 3 arm, randomized, double blind, parallel group treatment period employing doses of quetiapine 25 mg BID, 225 mg BID, and 150 mg TID. Dosage was to be titrated upwards during the 7 days. The third and final phase was open label extension treatment for patients who had completed at least 2 weeks of double blind treatment. Subjects were to be hospitalized for at least 2 weeks of double blind treatment. Screening was to be performed 3 to 7 days before randomization, and all psychotropic medication was to be stopped at least 2 days before the baseline assessments (performed at the time of randomization). Final determination of eligibility was to be made using the baseline assessment. Screening assessments included history and physical examinations, clinical laboratories, thyroid function tests, ECGs, pregnancy testing, and serum prolactin levels. Efficacy measures included the BPRS, SANS, and CGI. Safety monitoring included vital signs, clinical laboratories and EPS rating scales. Patients were to be seen weekly during the double blind period, and less often for open label treatment. Medication for stable conditions was permissable; the only permissable psychotropic medications were benzodiazepines and anti-EPS medication.

Analysis Plan

The protocol defined the primary efficacy measures as change from baseline in BPRS total score and CGI severity score at 6 weeks. Analysis of covariance was designated as the analytic method.

Protocol Amendments

The protocol was amended more than a dozen times. Many protocol amendments were specific to individual countries. Amendments concerned issues such as entry of women of child bearing potential, pharmacokinetic sampling, ophthalmology assessments, length of inpatient treatment, length of open label treatment, and various safety assessments. Additionally, there was a separate protocol for Canadian sites, although I was unable to discern any important differences between the two versions of the protocol.

Study Conduct/Outcome

Patient Disposition

A total of 678 patients enrolled in the study; 4 of these were enrolled at the site that was eventually excluded because of past allegations of research misconduct, leaving 674 patients.

Fifty six patients did not proceed to double blind treatment after the inital baseline period; of these, 25 withdrew consent and 31 failed to meet entry criteria. Thus, 618 patients were randomized to double blind treatment. Of these, 597 had at least one assessment after receiving study drug, and thereby constituted the intent to treat group (195 patients for quetiapine 225 mg BID, 204 for quetiapine 150 mg TID, and 198 for quetiapine 25 mg BID).

The table below presents the overall disposition of patients in the study. These figures refer to the set of all randomized patients, and it was not clear from the sponsor's presentation if these numbers were the same for the intent to treat group.

TABLE Number of patients and reasons for withdrawal (adapted from sponsor's electronic study report)

Reason for withdrawal	SEROQUEL 450 mg (bid) n	SEROQUEL 450 mg (tid) n	SEROQUEL 50 mg (bid) n
Lack of efficacy	60	64	80
Protocol non-compliance	7	6	6
Adverse event or intercurrent illness	12	7	7
Refused to continue or lost to follow-up	19	20	26
Total number of patients withdrawn	98	97	119

In this study, 47% of the quetiapine 225 mg BID group, 44% of the quetiapine 150 mg TID group, and 53% of the quetiapine 25 mg BID group withdrew prematurely. The rate of completion by week in the study is shown for each group in appendix table 7.2.4.2.

Demographics/Group Comparability

Appendix table 7.2.4.1 presents the demographic characteristics for patients in this study. Note that the sponsor provided these data for the set of all randomized patients, rather than the intent-to-treat sample, but in all likelihood the demographic profiles should be similar for the two patient sets. The patients in this study were overwhelmingly caucasian, with a mean age in the thirties. The treatment groups appeared to be similar demographically. Baseline total BPRS mean scores were close to 42 for all three groups.

Dosing Information

This was a fixed dose study.

Concomitant Medications

Zeneca presented information on concomitant use of benzodiazepines and anti-EPS drugs. These data are presented in the table below.

Concomitant Benzidiazepine and anti-eps medication (adapted from sponsor's electronic study report)

	quetiapine 450 mg (bid) (n = 200)	quetiqpine 450 mg (tid) (n = 209)	quetiapine 50 mg (bid) (n = 209)
Number of patients receiving benzodiazepines (%)	112 (56)	119 (57)	124 (59)
Number of patients receiving medication for EPS (%)	18 (9)	12 (6)	14 (7)

The proportion of patients receiving these types of medications was similar in all 3 treatment groups. Analysis of data on other concomitant medications was not provided.

Efficacy Results

Appendix tables present the results for the outcome measures of interest. For the mean BPRS total score, both the 225 mg BID and the 150 mg TID groups were superior at a statistically significant level to the 25 mg BID by the LOCF analysis. By the observed cases analysis, results were in favor of the 225 mg BID group, but 150 mg TID showed no statistically significant differences versus 25 mg BID.

On the CGI severity score analysis of covariance, data were not normally distributed, as evidenced by non-random residuals. Consequently, the sponsor opted for a categorical analysis approach, in which some categories were collapsed, using the Cochran Mantel Haenzel method. These results are displayed in an appendix table. The 225 mg BID group showed statistical superiority to the low dose group on this variable, but the 150 mg TID group did not.

On the BPRS psycosis cluster scores, the 225 mg BID group showed statistical superiority to the 25 mg BID group consistently on the LOCF analysis, and somewhat less consistently on the observed cases analysis. However, the 150 mg TID group was not superior to the 25 mg BID group at a statistically significant level for this measure.

For negative symptoms, results on the LOCF analysis favored the 225 mg BID group over the low dose by a statistically significant margin in the final weeks. Results were less consistent on the observed case analysis.

Miscellaneous Issues

Center 10 was excluded from the analysis after the sponsor learned that the investigator had been struck off the medical register in the U.K. because of allegations of misconduct during a previous study. This site had enrolled only 4 patients.

Trough plasma drug concentrations were to be obtained weekly; however, only 4 subjects in each group actually had such levels drawn, making conclusions about pharmacokinetic differences between the regimens problematic. In fact, the mean plasma concetration obtained from this small sample of patients was at times higher for the 50 mg/day group than for the high dose groups, a reflection of the wide individual variability in plasma drug concentrations.

Conclusions

This study supports efficacy of quetiapine 225 mg BID over 25 mg BID in the treatment of actively psychotic schizophrenic patients. The data provide marginal support for the efficacy of 150 mg TID over the low dose. One could speculate that patients in the BID dose group may have been more compliant than the subjects taking the TID doses; however, adequate plasma drug concentration data is lacking to evaluate this. With respect to negative symptoms, the efficacy of the higher dose treatment groups was not as consistently shown. On balance, this trial may be interpreted as supporting the efficacy of a BID dosing regimen, at least for a total dose of 450 mg.

7.2.5 Other Studies

Trial 0004 was a single center pilot study which, although small in sample size, demonstrated superiority of quetiapine over placebo. This was a randomized, double blind, placebo controlled study in which 12 schizophrenic inpatients participated. Eight recieved quetiapine and 4 received placebo; duration of treatment was 3 weeks and the median quetiapine dose was 200 mg. At endpoint, the mean BPRS score for the quetiapine group had decreased by 21 points, a statistically significant effect compared to placebo. This effect size was considerably larger than those seen in the pivotal studies.

Study 0015 was a one year, multicenter, randomized trial of relapse prevention, which compared haloperidol 12 mg/d to quetiapine 75 mg/d, 300 mg/d and 600 mg/d. Three hundred and one stable schizophrenic outpatients participated. Although the hypothesis was that a dose effect would be found, no treatment differences in rate of relapse were observed. Without a placebo group for determination of assay sensitivity, results from this trial are inconclusive.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

To examine the possibility that demographic characteristics influenced response, the sponsor provided no formal treatment by age, gender or race interaction analyses for the efficacy data. The sponsor did, however, display efficacy data separately by age category (over versus under age 40), by race and by gender, using BPRS and CGI data from trials 0013, 0006 and 0008. By inspection, there were no major differences in the efficacy results when subdivided in this fashion for race or gender. With respect to age, the effect size for drug relative to placebo appeared to be greater in the under 40 age group, paticularly for trial 0006. The clinical implications of this observation are unclear, however. Please refer to the discussion of demographic influences in DR. Hoberman's statistical review.

7.3.2 Choice of dose

In study 0013, all daily doses above 75 mg (i.e., 150, 300, 600 and 750 mg) showed efficacy relative to placebo with comparable effect sizes. However, in study 0008, the quetiapine high dose group, wtih a mean dose of around 500 mg/d, performed better than the low dose group having a mean dose of roughly 250 mg/d. In the proposed labeling, the sponsor indicates that the target dose should be 300 mg/d based on the above. In reaching this conclusion the sponsor seems to be giving more weight to study 0013 than to study 0008. However, study 0013 was the only adequate and well controlled study to use fixed doses.

7.3.3 Duration of Treatment

The efficacy of quetiapine was demonstrated in 6 week long controlled clinical trials. The long term relapse prevention trial, study 0015, failed to demonstrate efficacy for either quetiapine or the active control relative to the low dose quetiapine group. Thus, there is no data on efficacy beyond a treatment duration of 6 weeks.

7.4 Conclusions regarding efficacy data

Data from more than one adequate and well controlled study has shown quetiapine to be effective in the acute treatment of psychotic patients with schizophrenia. Data on long term relapse prevention are lacking. When the data are pooled according to age groups, the effect of the drug appears to be more robust in the subset of patients below 40 years of age.

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8.0 Integrated Review of Safety

8.1 Background and Methodology for Safety Review

Both the original NDA submission integrated phase II-III primary database and data from the NDA four month safety update were available for the safety review. Additionally, the sponsor provided safety data in manipulable electronic SAS format, for both the initial primary database and the 4 month safety update database. Additional information from certain foreign studies that were not part of the primary integrated database was considered, especially with respect to serious adverse events. The safety review focused on the phase II-III clinical experience as being the most relevant to the intended population for quetiapine treatment. Short term placebo controlled trials were the focus for evaluation of more common adverse events, since this data set provided a comparator group. The entire database of quetiapine exposures was searched for less common but more medically significant adverse events when appropriate. The sponsor's one year relapse prevention study, although lacking a placebo group, did include a haloperidol comparison group and also afforded an ability to examine dose effects during long term treatment, since three fixed doses of quetiapine were employed. In the discussion that follows, the convention for identifying individual patients will be to list their trial number , followed by their center number and individual patient number. Thus the designation 5077IL/0048;US-0010/1011 refers to a patient in study 5077IL/0048 (sometimes listed simply as 0048 for convenience), at U.S. center number 0010 with subject number 1011. Open label extension treatment is designated by the abbreviation OLE.

The NDA primary integrated database for Phase II-III studies included 2162 quetiapine treated patients, and the safety update submission included an additional 225 quetiapine patients, for a total of 2387 patients.

8.1.1 Deaths

Appendix table 8.1.1.1 lists all deaths associated with quetiapine treatment as of the cutoff date for the safety update (3/1/96). In my opinion, none of these deaths can be attributed exclusively to the effects of quetiapine. Specific cases and the possible influence of quetiapine on certain disease states are discussed under the relevant body system, in the review of systems that follows. Whether more aggressive medical management might have benefitted patient 0012/0045/4502, whose angina worsened over several days prior to his death from cardiac arrest, or patient 0012/0091/9103, who died with a progressive basilar artery thrombus and was apparently not transferred to a neurology service for 2 weeks after his initial neurological symptoms, is difficult to say.

Appendix table 8.1.1a lists certain other deaths reported outside the NDA or NDA safety update, for which only limited information is available (from IND safety reports, the IND annual report, and an interim IND safety summary that Zeneca submitted 9/20/96)

Table 8.1.1.2 in the appendices shows the overall mortality in the Phase II-III integrated quetiapine database. There is no suggestion of excessive mortality associated with quetiapine treatment from these data.

8.1.2 Other Serious Adverse Events

Zeneca provides the following definition of serious adverse event in the Integrated Summary of Safety: "any event that suggests a significant hazard, contraindication, side effect, or precaution."

This category is broader than the more explicit FDA definition of a serious adverse experience (as one that meets any of the following descriptions: fatal; life threatening; permanently disabling; leading to hospitalization; cancer; overdose; or congenital anomaly). However, it would presumably include all events meeting the more specific FDA definition.

Designation of a clinical trial event as serious was a judgement of the Zeneca physician monitor early in the development program, but subsequent to the End of Phase II meeting with FDA the sponsor permitted the clinical investigator to make this determiniation.

Zeneca states in the Integrated Summary of Safety that certain events were automatically considered serious: those involving the COSTART terms convulsion, grand mal convulsion, myoclonus (if used for investigators' terms of tonic and/or clonic convulsions), syncope, suicide attempt, overdose, neuroleptic malignant syndrome, and agranulocytosis.

Among the 343 quetiapine treated subjects in the Phase I studies in the primary integrated database, the sponsor reported that 11 (3.2%) had seriious adverse events. Among the 2,387 quetiapine treated patients in the Phase II-III primary integrated database, there were 180 (7.5%) with serious adverse events (subjects and patients could have more than one serious adverse event). Specific serious adverse events will be discussed under the Review of Systems.

8.1.3 Dropouts

8.1.3.1 Overall Profile of Dropouts

Overall, in the initial NDA primary integrated database, 80% of quetiapine treated patients (1731 out of 2162) in Phase II-III trials discontinued treatment prematurely. The comparable figure for Phase I studies was 14% (42 out of 300 subjects). (The sponsor did not provide data on the overall pattern of dropouts for the safety update database.) The table below displays the reasons for premature discontinuation from studies in the Phase II-III integrated database, not including the safety update data.

TABLE Number of subjects withdrawn and reason for withdrawal in Phase II-III trials (adapted from sponsor's electronic submission)

Reasons for withdrawal	Number of subjects withdrawn (%)		
	Quetiapine (n = 2162)	Comparison drugs (n = 420)	Placebo (n = 206)
Total number of subjects withdrawn	1731 (80.1)	177 (42.1)	126 (61.2)
Lack of efficacy	1033 (47.8)	68 (16.2)	100 (48.5)
Subject refused to continue or was lost to follow-up	398 (18.4)	47 (11.2)	14 (6.8)
Adverse event or intercurrent illness	154 (7.1)	45 (10.7)	7 (3.4)
Subject withdrew consent	4 (0.2)	8 (1.9)	0
Protocol noncompliance	118 (5.5)	5 (1.2)	0
Other*	24 (1.1)	4 (0.9)	5 (2.4)

* Zeneca reports that 2 of the 24 patients listed as other acutally dropped out for adverse experiences (eye disturbance and postural hypotension).

The majority of patients withdrawn discontinued for lack of efficacy. The group most relevant for the safety review is, of course, the 154 patients who discontinued quetiapine because of medical problems, either intercurrent illness or adverse events. Note that investigators were required to indicate if an adverse event was a reason for premature discontinuation; more than

one adverse event could be so designated (per telecon with sponsor 12/2/96).

It may be more informative to consider dropouts from a pool of short term trials, since the data above combines double blind and open label treatment. The sponsor provided the following table of reasons for withdrawal from short term placebo controlled trials (studies 0004, 0006, 0008, 0013).

Table Reasons for withdrawal from short term placebo controlled trials (adapted from sponsor's ISS)

Reasons for withdrawal	Number of subjects withdrawn (%)	
	Quetiapine (n = 510)	Placebo (n = 206)
Total number of subjects withdrawn	271 (53.1)	126 (61.2)
Lack of efficacy	182 (35.7)	100 (48.5)
Subject refused to continue or was lost to follow-up	49 (9.6)	14 (6.8)
Adverse event or intercurrent illness	19 (3.7)	7 (3.4)
Protocol noncompliance	8 (1.6)	0
Other	13 (2.5)	5 (2.4)

Note that withdrawal for lack of efficacy was more common among placebo patients, while withdrawal for adverse events was roughly equivalent between the two groups.

8.1.3.2 Adverse Events Associated with Dropout

Overall, a total of 176 out of 2387 (7.4%) patients treated with quetiapine in the integrated primary database withdrew prematurely because of adverse events.

To examine the adverse events commonly cited as reasons for discontinuation, it may be useful to focus on the pool of controlled clinical trials, since this subset of data includes comparator groups with roughly comparable exposure. This would not be the case if one considers the entire quetiapine exposure database, which includes much exposure in uncontrolled open label treatment, making comparisons to control groups problematic. The table below displays the more common adverse events reported as reasons for premature discontinuation among quetiapine treated patients in controlled studies.

TABLE

Adverse events leading to withdrawal of 3 or more subjects from treatment with quetiapine in controlled Phase II-III trials (adapted from sponsor's electronic ISS) Control groups are included for comparison. Data is from studies 0004, 0006, 0007, 0008, 0012, 0013, 0014, and 0015.

COSTART term	Number of subjects withdrawn (%)		
	Quetiapine (n = 1710)	Active Controls (n = 420)	Placebo (n = 206)
Total number of subjects withdrawn because of adverse events*	86 (5.0)	45 (10.7)	6 (2.9)
Somnolence	24 (1.4)	4 (1.0)	0
Postural hypotension	7 (0.4)	0	0
SGPT increased	6 (0.4)	1 (0.2)	1 (0.5)
SGOT increased	5 (0.3)	0	1 (0.5)
Hypotension	5 (0.3)	0	0
Depression	5 (0.3)	4 (1.0)	0
Leukopenia	4 (0.2)	0	0
Dizziness	4 (0.2)	0	0
Suicide attempt	3 (0.2)	2 (0.5)	0
Tachycardia	3 (0.2)	2 (0.5)	1 (0.5)
Gamma glutamyl transpeptidase increased	3 (0.2)	0	0
Alkaline phosphatase increased	3 (0.2)	0	0
Agitation	3 (0.2)	2 (0.5)	0

*Subjects may have had more than one adverse event leading to withdrawal.

Specific adverse experiences associated with dropout will be described under the review of systems.

8.1.4 Other Search Strategies

Zeneca analyzed the incidence of particular adverse events and sets of adverse events in terms of subect years of exposure for quetiapine and control treatments. The following table shows the results of the sponsor's analysis of these selected events. Exposures for quetiapine are shown with and without data from the safety update. Specific events of concern are discussed later in the review of systems.

TABLE Incidence of important groups of selected adverse events (adapted from sponsor's electronic ISS)

Adverse event group**	Quetiapine (n = 2162) SY = 585.1		Quetiapine wtih safety update (n = 2387) SY = 865.3		Haloperidol (n = 320) SY = 42.3		Chlorpromazine (n = 100) SY = 9.2		Placebo (n = 206) SY = 14.6	
	k (%)*	ER	k (%)*	ER	k (%)*	ER	k (%)*	ER	k (%)*	ER
Syncope	21 (1.0)	3.7	26 (1.1)	3.0	1 (0.3)	2.4	1 (1.0)	10.9	0	0
Convulsion	9 (0.4)	1.5	18 (0.8)	2.1	2 (0.6)	4.7	2 (2.0)	21.8	1 (0.5)	6.9
Neuroleptic malignant syndome	2 (0.1)	0.3	2 (0.1)	0.2	0	0	0	0	0	0
Suicidality	34 (1.6)	5.8	40 (1.5)	4.6	6 (1.9)	14.2	0	0	2 (1.0)	13.7
Depression	38 (1.8)	6.5	43 (1.8)	5.0	5 (1.6)	11.8	0	0	4 (1.9)	27.5
Cataract	15 (0.7)	2.6	16 (0.7)	1.8	1 (0.3)	2.4	0	0	0	0
Thyroid disorder	10 (0.5)	1.7	15 (0.6)	1.7	0	0	0	0	0	0
Rash and allergic phenomena	81 (3.7)	13.8	96 (4.0)	11.1	13 (4.0)	30.7	5 (5.0)	54.5	9 (4.4)	61.8
Edema	27 (1.2)	4.6	44 (1.8)	5.1	1 (0.3)	2.4	0	0	1 (0.5)	6.9
Leukopenia	43 (2.0)	7.3	48 (2.0)	5.5	0	0	1 (1.0)	10.9	0	0
Leukocytosis	11 (0.5)	1.9	13 (0.5)	1.5	0	0	1 (1.0)	10.9	5 (2.4)	34.3
Eosinophilia	6 (0.3)	1.0	8 (0.3)	0.9	1 (0.3)	2.4	0	0	0	0
Thrombocytopenia	2 (0.1)	0.3	2 (0.1)	0.2	1 (0.3)	2.4	0	0	0	0
Increased liver function tests	71 (3.2)	12	76 (3.2)	8.8	0	0	4 (4.0)	43.6	4 (1.9)	27.5

*Number of subjects with adverse events (%).
SY = Subject years of follow up
ER = Event rate per 100 subject-years exposure
**Costart terms used in search, if more than the term listed:
depression: depression, depression for investigators' terms that do not indicate suicidal ideation, depression psychotic
suicidality: suicidality, depression for investigators' terms that indicate suicidal ideation, suicide attempt, overdose, intentional injury
syncope: syncope, syncope for investigators terms that do not indicate seizure
convulsion: convulsion, grand mal convulsion, myoclonus for investigators' terms of tonic convulsion or clonic convulsion, syncope for investigators terms that indicate seizure
increased liver function tests: increased liver enzyme tests, SGOT increased, SGPT increased, alkaline phosphatase increase, gamma glutamyl transpeptidase increased, bilirubinemia
leukopenia: leukopenia, agranulocytosis
thyroid disorder: thyroid disorder, hypothyroidism, hormone level altered
rash:rash, maculopapular rash, vesiculobullous rash, allergic reaction, pruritus, angioedema
edema: edema edema facial, edema generalized, edema peripheral, edema larynx, lymphedema
cataract: cataract , cataract specified, eye disorder for investigators' terms that indicate cataract

8.1.5 Adverse Event Incidence Tables

8.1.5.1 Approach to Eliciting Adverse Events in the Development Program

In the integrated summary of safety, Zeneca states that an adverse event was considered as any pathologic or unintended change in structure, function, or chemistry of the body associated with use of the drug. Zeneca employed an adverse event thesaurus based upon the standard COSTART dictionary of adverse events. I found no indication that adverse event questionnaires were used in the clnical trials, thus I presume that all adverse events reported were spontaneously volunteered. The exception was use of rating scales for documentation of extrapyramidal symptoms (EPS). In a schizophrenic population, reliance on spontaneously volunteered complaints may result in underreporting, as has been observed in clinical trials which used both spontaneously volunteered reports and reports elicited by an adverse event checklist.

8.1.5.2 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

From the sponsor's electronic CANDA version of the primary integrated database, I was able to create a spreadsheet showing the investigator's adverse event terms alongside the COSTART

terms to which they were coded. A random audit of these revealed no obvious systematic misclassification of adverse event terms. On occassion, cases that were individually reviewed were reclassified (e.g., certain serious adverse events described under review of systems).

8.1.5.3 Selecting the Key Adverse Event Tables for Characterizing the Adverse Event Profile

One approach to evaluating the more common adverse events is to pool data from all the short term placebo controlled trials (studies 0004, 0006, 0008, and 0013). The sponsor's table from the integrated summary of safety displaying the data obtained in this manner is presented in the appendix as table 8.1.5.3. The minimum incidence for events shown was 1% in quetiapine treated patients, and events which were actually more common in placebo treated patients have been omitted.

Appendix table 8.1.5.4 displays other adverse events arising among quetiapine treated patients in the primary integrated database of 2162 subjects. Data from the 4 month safety update is not included. Note that this table was adapted from the sponsor's proposed labeling, and that adverse event terms displayed in the 1% table are ommitted. In addition, the sponsor has chosen to omit certain other adverse event terms, i.e., "those events for which causality has not been established, and those event terms which were so general as to be uninformative." The sponsor has not provided a list of the adverse event terms deleted for these reasons.

8.1.5.4 Identifying Common and Drug-Related Adverse Events

A number of methods can assist in determing which adverse events are common in incidence and possibly causally related to the drug. One approach is statistical.. As shown in the table above, statistical significance testing was performed on the incidences of adverse events occurring at a rate of 1% or more. (This should not be regarded as hypothesis testing in the ususal sense, particularly since there was no accounting for multiple compariisons. Rather, the p-values can be regarded as reflecting the magnitude of difference in incidence between the quetiapine and placebo groups.) The following adverse events had incidences for which the p-value comparing quetiapine to placebo was less than or equal to 0.05:

Dizziness, Somnolence, SGPT increased, SGOT increased, Weight gain, Dry mouth, Abdominal pain.

A second method is to determine which adverse events are at least twice as frequent among drug treated patients as among placebo treated patients, and which are also observed at an incidence of at least 5 per cent with the drug. These are often referred to as the "common and drug related" adverse events. Applied to the table above, this method yields the following list of common, drug related adverse events:

Dizziness, SGPT increased, dry mouth, dyspepsia, postural hypotension.

Note that dizziness, SGPT increased, and dry mouth appear in both lists.Specific adverse events will be discussed under the review of systems.

8.1.5.5 Additional Analyses and Explorations

Dose Response

The short term placebo controlled fixed dose study, trial 0013, permitted analysis of dose

response. As previously described, this was a 6 week fixed dose study using doses of 75, 150, 300, 600, and 750 mg/d, with roughly 50 patients per group. Zeneca performed an analysis of dose response for adverse events occurring at an overall incidence of 3% among quetiapine treated patients, using logistic regression. Dyspepsia, weight gain, and abdominal pain showed p-values less than 0.05, and dry mouth, postural hypotension, and leukopenia showed marginal p-values (between 0.1 and 0.05). Extrapyramidal symptoms did not show a dose related pattern. In addition, the long term relapse prevention trial, study 0015, employed doses of 75, 300 and 600 mg/d with approximately 90 patients in each dose group. This data permits consideration of treatment emergent adverse experiences ariising in long term therapy. Here, a logistic regresssion analysis of dose response produced statistically significant p-values for the adverse events of nervousness and weight gain. Additionaly, marginal p-values were obtained for the adverse events of hypertonia, cataract specified, and dry mouth. Not e that weight gain and dry mouth showed some indication of dose relatedness in both long term and short term treatment data.

Demographic Analyses

The sponsor compared adverse event incidences from the pool of short term placebo controlled tirals with respect to age, race and gender. For this analysis, the odds ratios (quetiapine versus placebo) by demographic subgroup were determined for every adverse event having an overall quetiapine incidence of 1%. Then, the Breslow-Day test for homogeneity of the odds ratio across the subgroups was applied.

For the sponsor's comparisons by demographic group, the following numbers of patients contributed data:

Gender
Women: n=124 quetiapine, n=47 placebo
Men: n=386 quetiapine, n=159 placebo

Age
Under 40: n=317 quetiapine, n=125 placebo
40 and over : n=193 quetiapine, n=81 placebo

Race
White: n=345 quetiapine, n=143 placebo
Black: n=121 quetiapine, n=47 placebo
Other: too few to analyze

By the Breslow-Day test, no adverse event showed a significant difference in odds ratio by gender at a probability level of 5%. There was a marginally significant difference for the event dyspepsia (p=0.09), with a higher odds ratio for men.

For age subgroups, somnolence showed a higher odds ratio in younger patients (p=0.05), as did headache (p=0.07) and rash (p=0.08).

For race, the Breslow Day test showed a significant difference for myalgia, which was associated with quetiapine treatment in whites, but was not reported in blacks receiving quetiapine. Additionally, dry mouth showed a higher odds ratio in whites than in blacks (p=0.08).

In my opinion, these differences are not likely to be clinically meaningful, and may even be due to

chance.

8.1.6 Laboratory Findings

8.1.6.1 Extent of Laboratory Testing in the Development Program

The primary source for the review of laboratory findings will be the integrated Phase II-III studies; I will not focus on laboratory findings from phase I studies, unless a significant adverse event was associated with a laboratory abnormality.

Appendix table 8.1.6.1 displays the specific laboratory measures obtained in each triial in the original NDA submission. This table displays only which clinical laboratories were obtained, not how frequently they were obtained. In the short term placebo controlled trials clinical laboratories were obtained at least weekly (more often for study 0004).

8.1.6.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

The review of clinical laboratory data to be presented here will focus on data pooled from the set of short term placebo controlled trials, consisting of studies 0004, 0006, 0008, and 0013. With the exception of study 0004, a 3 week study with relatively few patients, these studies were 6 weeks in duration. In my judgement, this pool of studies represents the best choice for review of clinical laboratory findings, since the placebo control group affords an opportunity for comparison. Additionally, the duration of exposure is not a confounding variable as it would be if long term quetiapine treatment data were to be compared to placebo data involving briefer treatment; in these studies, duration of treatment was more consistent between quetiapine and placebo.

8.1.6.3 Standard Analyses and Explorations of Laboratory Data

8.1.6.3.1 Analyses Focused on Measures of Central Tendency

Appendix tables 8.1.6.3.1(a, b and c) display the mean changes from baseline for quetiapine and placebo groups with respect to hematology, clinical chemistry, and urinalysis values. the sponsor did not perform hypothesis testing on these data. By inspection, notable findings associated with quetiapine treatment include a roughly 10% increase in cholesterol and triglycerides, and changes in some thyroid function tests. These findings will be discussed under the review of systems.

8.1.6.3.2 Analyses Focused on Outliers

Appendix table 8.1.6.3.2 presents the The sponsor's criteria for defining laboratory abnormalities as clinicallysignificant. These criteria, although necessarily arbitrary, appear reasonable in my opinion. Appendix tables 8.1.6.3.2 a,b and c display the proportion of patients meeting these criteria for each treatment group in short term placebo controlled trials. For the following parameters, quetiapine treatment was associated with a statistically significantly greater proportion of patients meeting the criterion values compared to placebo: low total T4, high ALT, high triglycerides, high reverse T3. Statistical significance was marginal (i.e., p value between 5 and 10%) for these additional parameters: low free T4, low hematocrit. With respect to hematocrit, there did not appear to be a similar excess of quetiapine patients having low hemoglobin.

8.1.6.3.3 Dropouts for Laboratory Abnormalities

In the primary phase II-III integrated database of 2387 quetiapine treated patients, the following laboratory abnormalities accounted for premature discontinuation in 0.3% or more of patients:

Leukopenia	0.6%
ALT increased	0.4%
AST increased	0.3%

Zeneca provided narrative summaries and case report forms for all patients prematurely discontinued because of laboratory abnormalities. These cases will be discussed under the appropriate body system in review of systems.

8.1.6.4 Additional Analyses and Explorations

The sponsor submitted a supplemental analysis of thyroid function test data from controlled clinical trials. Zeneca also submitted a special analysis of white blood cell laboratory abnormalities associated with quetiapine treatment. These analyses will be discussed under the Review of Systems.

8.1.7 Vital Signs

8.1.7.1 Extent of vital sign testing in the development program

The discussion of vital sign data will draw primariily upon data presented in the original integrated summaryof safety, as there was little additional data presented in the safety update.

Appendix Table 8.1.7.1 shows the type of vital sign assessments performed for each trial in the integrated database (not including the safety update).

8.1.7.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

As with the laboratory data, the most informative pool of vital sign clinical trial data for comparing quetiapine and placebo treated patients will be the short term placebo controlled trials. The approach will be similar to that outlined above for laboratory data.

8.1.7.3 Standard Analyses and Explorations of Vital Sign Data

8.1.7.3.1 Analyses Focused on Measures of Central Tendency

Appendix table 8.1.7.3.1 summarizes mean vital sign changes from baseline for the pool of short term placebo controlled triials. Both quetiapine and placebo data are shown. Zeneca performed no hypothesis testing on these data. Overall, there was a modest mean increase in pulse (both standing and supine) associated with quetiapine treatment, and a mean weight increase of over two kgs, relative to placebo patients. On average, vital signs did not show much in the way of orthostatic changes.

8.1.7.3.2 Analyses Focused on Outliers

Appendix table 8.1.7.3.2 displays the criteria that Zeneca chose for defining vital signs as potentially clinically significant. These appear reasonable to me, although they are necessarily arbitrary. As seen in appendix table 8.1.7.3.2b, the proportion of quetiapine patients with a high standing pulse was statistically significant compared to the placebo group, consistent with an

orthostatic drug effect. The proportion of quetiapine patients with increased weight was also statistically significant compared to placebo.

8.1.7.3.3 Dropouts for vital sign Abnormalities

The following table enumerates patients who dropped out for vital sign abnormalities in the original NDA submission database. The sponsor did not provide a similar table for the safety update data.

Table: Subject withdrawals for abnormal vital signs or weight measurements during Phase II-III controlled trials (does not include safety update data. Adapted from sponsor's electronic ISS submission)

COSTART term	Quetiapine (n = 1710)	Placebo (n = 206)	Haloperidol (n = 320)	Chlorpromazine (n = 100)
	Number of subjects (%)	Number of subjects(%)	Number of subjects (%)	Number of subjects (%)
Hypotension	5 (0.42)	0	0	0
Postural hypotension	7 (0.59)	0	0	0
Hypertension	0	0	0	1(1.0)
Weight gain	1 (0.08)	0	0	0
Syncope	2 (0.17)	0	0	0
Tachycardia	3 (0.25)	1 (0.4)	0	2 (2.0)
Sinus bradycardia	1 (0.08)	0	0	0

Uncontrolled Trials (n=1256)

	Number of subjects (%)
Cardiovascular	
Bradycardia	1 (0.1)
Heart arrest	1 (0.1)
Hypotension	1 (0.1)
Postural hypotension	4 (0.3)
Syncope	1 (0.1)
Tachycardia	2 (0.2)
Total subjects	10 (0.8)

The sponsor provided narrative summaries of these cases. Specific adverse events will be discussed under the review of systems.

8.1.7.4 Additional Analyses and Explorations

None to report.

8.1.8 ECGs

8.1.8.1 Extent of ECG testing in the development program

Twelve lead electrocardiogram monitoring was performed in 8 of the primary integrated database phase II-III clinical trials (see appendix table 8.1.8.1), and during open label treatment with quetiapine at U.S. sites. I found no reference to any Holter monitoring studies.

8.1.8.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

As with the clinical laboratory and vital sign analyses, the primary data set for consideration of ECG findings will be the pool of short term placebo controlled Phase II-III trials. This provided roughly 400 quetiapine patients with baseline and on treatment ECG tracings, and roughly 150 placebo patients for comparison.

8.1.8.3 Standard Analyses and Explorations of ECG Data

8.1.8.3.1 Analyses Focused on Measures of Central Tendency

Appendix table 8.1.8.3.1 presents a summary of mean changes from baseline for ECG parameters with quetiapine treatment in Phase II-III studies. Except for a slight mean increase in heart rate, there were no notable mean changes in ECG parameters associated with quetiapine. The sponsor perfored no statistical hypothesis testing on these data.

8.1.8.3.2 Analyses Focused on Outliers

Appendix table 8.1.8.3.2a shows the sponsor's criteria for considering ECG abnormalities possibly clinically significant. Applying these criteria to the short term placebo controlled trial data, there were no statistically significant differences between the quetiapine and placebo patient groups for the numbers of patients meeting these criteria, as seen in appendix table 8.1.8.3.2b. Note that the sponsor chose a relatively conservative criterion value for QTc, i.e., 450 msec.

8.1.8.3.3 Dropouts for ECG Abnormalities

The following table enumerates the patients discontinued for ECG abnormalities. The sponsor did not provide a similar table for the safety update data.

TABLE ECG-Related Withdrawals (Adapted from sponsor's ISS; does not include safety update)

Controlled trials

	Quetiapine n = 1710	Placebo n = 206	Haloperidol n = 320	Chlorpromazine n = 100
Tachycardia	3	1	0	2
Bradycardia	1	0	0	0

Uncontrolled trials (n = 1256)	
Tachycardia	2
Bradycardia	1
ECG abnormal (nonspecific ST-T changes)	1
Heart arrest (fatal)	1
Pericarditis (later deemed normal ECG variant)	1

The sponsor provided narrative summaries of these cases. The specific adverse events involved will be discussed under the review of systems.

8.1.8.4 Additional Analyses and Explorations

There were none to describe.

8.1.9 Special Studies

In pharmacodynamic interaction studies to explore the psychomotor effects of quetiapine combined with ethanol (study 0024) and lorazepam (study 0027), involving 10 subjects each, the combination exacerbated the psychometric deficits observed with either ethanol or lorazepam alone.

8.1.10 Withdrawal Phenomena/Abuse Potential

The sponsor did not perform any studies to determine the abuse potential of quetiapine, or the safety of sudden versus gradual discontinuation of treatment.

8.1.11 Human Reproduction Data

The following table summarizes pregnancy experiience with quetiapine.

Table Summary of pregancy exposures with quetiapine (from sponsor's 2/12/97 submission)

Trial;subject	age	quetiapine exposure	Outcome and comments
5077IL/0012:4515		1st trimester	Elective abortion at 5 weeks
5077IL/0061;113	18	500 mg/d for 3-4 weeks of 1st trimester	Healthy baby girl

No conclusions can be drawn from such a limited number of pregnancy exposures.

8.1.12 Overdose Experience

The sponsor defined an overdose as an ingestion of 900 mg or more of quetiapine. Zeneca performed a search of the integrated safety database including the safety update data and found a total of 7 quetiapine overdoses of 900 mg or more. Additionally, an elderly subject mistakenly received 600 mg and a 5 year old boy ingested 600 mg. These cases are described in the following table.

Table Summary of overdoses with quetiapine

Trial;subject	Age	Sex	over-dose mg	Concomitant drugs	Comments
0014OLE; UK-0067/6707	42	m	2800	diazepam 1000 mg	Emesis induced, recovered after 24 hours
5077IL/0048;US-0010/1011	73	f	600		accidental overdosein patient with dementia. Somnolence and hypotension; treated with sorbitol and charcoal, recovered withing hours
5077IL/0012 OLE:0001/0108	23	f	1500		No information on treatment or signs and symptoms. Patient recovered and contiued in trial.
5077IL/0012ole;0003/0301	36	m	1200		No symptoms reported and subject continued in trial
5077IL/0012 OLE;0035/3504	25	f	2000	temazepam 50 mg	Patient hospitalized and received IV fluids. Two to three days after overdose developed increased CPK, rash, back pain, fever, myalgia, and buccal dyskinesia; recovered.
5077IL/0012 OLE;0084/8414	36	f	6400	pimozide, chlorazepate, bipiriden, asa, diclofenac, paracetamol, haloperidol, codeine, dexchlor-pheniramine	Hospitalized in a coma and placed on mechanical ventilation. Developed elevated LFTs, aspiration pneumonia and ARDS. Recovered after 11 weeks in hospital.
5077IL/0013 OLE;0011/1104	25	m	9300		obtundation, sinus tachycardia to 140 bpm, hypokalemia, (2.8 mmol/l), 1st degree heart block. Treated with lavage and charcoal., cathartic, Kcl, diazepam for agitation,; recovered
5077IL/0014 OLE;0026/2610	28	f	6500	tenox 600 mg	Patient became unconcious but recovered; no further details
not a subject	5	m	600		Developed sedation, hospitalized, recovered

This limited number of reported overdoses does not seem to indicate extraordinary toxicity from the compound. Several cases involved overdose on multiple medications.

8.2 Review of Systems

8.2.1Cardiovascular

8.2.1.1 Adequacy of assessment of cardiovascular system effects

Orthostatic vital signs and electrocardiograms were obtained during the majority of clinical trials. Cardiovascular adverse events were recorded in the usual fashion. I am aware of only one patient who had a holter monitor recording, which was obtained as part of a syncope evaluation. On balance, the evaluation of the cardiovascular system appears to have been adequate.

8.2.1.2 Cardiovascular Adverse events Considered Possibly, probably, or Definitely Related to Quetiapine

Postural hypotension and syncope

Quetiapine's alpha adrenergic blocking properties suggest that it may have a capacity to induce orthostatic hypotension. In the pool of short term controlled trials, dizziness and postural hypotension were among the common and drug related adverse events. The statistical analyses of vital sign data did not show much evidence for orthostatic hypotension, except that the increase in the proportion of quetiapine patients meeting the critierion for high standing pulse was statistically significant versus placebo patients. In the pool of all controlled trials, postural hypotension was the second most common reason for quetiapine patients discontinuing prematurely; no patients from the control groups discontinued prematurely for postural hypotension.

Syncope is an event that is sometimes attributed to postural hypotension. The sponsor's analysis of adverse events judged to represent syncope (see table in section 8.1.4 above) showed the following:

TABLE Incidence of syncope (adapted from sponsor's electronic ISS)**

Quetiapine (n = 2162) SY = 585.1		Quetiapine wtih safety update (n = 2387) SY = 865.3		Haloperidol (n = 320) SY = 42.3		Chlorpromazine (n = 100) SY = 9.2		Placebo (n = 206) SY = 14.6	
k (%)*	ER	k (%)*	ER	k (%)*	ER	k (%)*	ER	k (%)*	ER
21 (1.0)	3.7	26 (1.1)	3.0	1 (0.3)	2.4	1 (1.0)	10.9	0	0

*Number of subjects with adverse events (%).
SY = Subject years of follow up ER = Event rate per 100 subject-years exposure
** syncope, for investigators terms that do not indicate seizure

In my own search of the adverse event data including the safety update data, (electronic search using data set 4msudbol/adversev), there were 1/320 haloperidol patients, 1/100 chlorpromazine patients, no placebo patients, and 27/2387 (1.1%) quetiapine treated patients having adverse events with the Costart term syncope. Among the patients so identified, the median time on quetiapine when syncope occurred was 14 days, while the mean was considerably greater (88 days). Thus syncope is frequently encountered early in treatment, but not always so. Review of the narrative summaries for cases of syncope revealed that in a number of cases the subject was noted to have postural hypotension, but in other cases no orthostatic vital signs were obtained, so that generalizations about the association of syncope with vital sign changes are difficult.

Increased heart rate

Although palpitation was not a common, drug related adverse events in the short term controlled studies, there was a 3-4 bpm mean increase in both supine and standing pulse in the short term controlled trials among quetiapine patients, at endpoint, compared to a 1-2 bpm increase with placebo, suggesting that the increase in heart rate is not necessarily limited to the standing position. In addition, ECG data from controlled trials showed a mean increase in heart rate of 7 bpm for quetiapine compared to 1 bpm for placebo, at endpoint. With respect to dose dependency, in study 0013, mean increase in supine pulse from baseline to endpoint for the various quetiapine dose groups ranged from 2-6 bpm, but without a clear dose relationship.

Similarly, in the same study the increase in heart rate on ECG ranged from 2-10 bpm among quetiapine dose groups, but without a clear dose related trend.

One subject, 0048/0008/0810, a 77 year old man with pre-existing cardiac disease, developed persistent tachycardia (roughly 15 0 bpm) for which a cardiologist was unable to find and etiology; the tachycardia resolved 3 days after discontinuing quetiapine. Patient 0013/0018/1808, a 28 year old male, discontinued quetiapine because of tachycardia; he complained of episodes of palpitation, dizziness, weakness and dyspnea; only mild sinus tachycardia was ever documented.

QT prolongation

Preclinical data does not provide evidence of a QT prolonging effect of quetiapine in the animals studied; please refer to the pharmacology review for details.

Two cases involving QT prolongation merit description. Patient 0048/0013/1301, a 73 year old female with dementia, suffered syncope after 5 days on quetiapine (dose 25 mg/d); concomitant medication was carbamazepine. The patient was hospitalized for evaluation; an ECG that same day showed a prolonged QT interval (QTc 0.612 sec). The QTc interval returned to 0.412 a few days later while the patient continued quetiapine. A cardiology consultation was obtained, and the patient underwent an echocardiogram (normal) and Holter monitoring (also normal). No etiology other than quetiapine treatment was specified for the syncope. An additiional patient, 0048/0013/1305, a 69 year old female with vascular dementia, was hospitalized after 12 weeks on quetiapine (dose 275 mg/d) for a prolonged QTc interval of 606 msec (baseline QTc =409 msec). A repeat ECG showed a QTc interval of 476 msec; quetiapine was discontinued and the patient's QTc remained below 500 msec. An echocardiogram was normal. In my opinion, these cases in themselves are inconclusive regarding a causal relationship to quetiapine treatment.

In the pool of short term controlled trials, there was little mean change in QTc interval (for all quetiapine doses combined); nor was there a significant number of quetiapine patients with treatment emergent QTc prolongation beyond 500 msec in comparison to placebo (please see appendix tables 8.1.8.3.1 and 8.1.8.3.2). Thus from this analysis there was no signal of QT prolongation, and this is what Zeneca notes in their draft labeling.

With the electronic CANDA database, it was possible to perform a broader search for clinically significant QT prolongation. I was able to search the entire controlled Phase II-III trial database for treatment emergent QTc prolongation, using the ISS database and ECG data set. This was the largest database for which electronically formatted ECG data was provided (i.e., no open label data was included). Patients with baseline QTc intervals greater than or equal to 500 msec, and those missing a baseline QTc interval, were excluded. The remainder constituted the number of patients at risk for documented treatment emergent QTc prolongation $\geq$ 500 msec. Results are shown below.

Treatment group	Patients at risk	Pts with at least one QTc ≥ 0.5 sec N (%)	Mean no. of ECG tracings per pt in group
Quetiapine	698	10 (1.4)	3.1
Placebo	151	2 (1.3)	3.1
Chlorpromazine	88	2 (2.3)	3.5
Haloperidol 12 mg	37	0	3.0

Thus, as with the smaller pool of short term controlled studies, the data did not provide evidence for a QT-prolonging effect of quetiapine.

In the analyses described thus far, all quetiapine doses were combined. To examine the possibility that a QT prolonging effect might occur only at relatively high doses, data from the two fixed dose controlled studies was considered.

Study 0013: In this short term fixed dose trial with doses up to 750 mg, there was a mean increase from baseline to endpoint in QTc interval of 10 msec in the 600 mg group; this was statistically significant in comparison to placebo. However, there were negligible mean changes in the other quetiapine dose groups, including the 750 mg group; thus the data were not consistent with a dose response pattern. From the CANDA electronic dataset ISS/QTc Summary, searched with the JMP statistical application, no patients in the study had treatment emergent QTc above 0.500 sec.

Study 0015: In the long term fixed dose, the largest mean increase from baseline for QTc interval among any treatment groups at endpoint was 0.01 sec, in the high dose (600 mg) group; the corresponding values for the other treatment groups were 0.00 sec for quetiapine 300 mg, -0.01 sec for quetiapine 75 mg, and -0.01 sec for haloperidol 12 mg. No statistical comparison between groups was provided for this study. From the CANDA electronic dataset ISS/QTc summary, four patients in the 600 mg group had treatment emergent QTc greater than or equal to 500 msec, compared to one each in the 300 and 75 mg groups and none in the haloperidol group.

Thus, the data from study 0015 could be interpreted as representing a QT prolonging effect at the high dose; however, the sponsor did not provide a statistical comparison between dose groups, so inferences are limited. Also, the data from study 0013 was not consistent with a dose dependent effect.

On balance, the data do not consistently reflect a QT prolonging effect of quetiapine.

Deep vein thrombophlebitis and thrombosis

Three quetiapine treated patients developed deep vein thrombophlebitis (DVT), and one patient developed an intracardiac thrombus despite the lack of obvious cardiac disease. The cases are summarized below.

0048/US0013/1307	66 year old female with deep veen thrombosis of lower extremity after 5 mo. on quetiapine;patient was receiving conjugated estrogen
0015 OLE/0005/0502	63 year old woman developed deep vein thrombosis after 180 days on quetiapine (this patient had other serious adverse events also: intestinal obstruction, breast carcinoma, sepsis, described under the corresponding body system)
0008/0035/0808	42 year old male on quetiapine for 16 days (dose 250 mg) developed thrombophlebitis of left lower extremity and was treated with anticoagulation; discontinued quetiapine. Past history of thrombophlebitis.
0012 OLE/0091/9143	46 year old male on quetiapine 400 mg/d for 55 days developed right sided hemiplegia, diagnosed as having a completed stroke; echocardiogramshowed a left ventricle thrombus; no significant past medical history

In addition, there was one death from cerebral vascular disease in which the patient was found to have a basilar artery thrombus at autopsy; this patient had no significant past medical history (patient 0012/0023/2303). Also, an IND safety report subsequent to the NDA submission (see appendix table 8.1.1.1) reported the death of a 69 year old man from pancreatic cancer; this patient had DVT, but of course DVT has been associated with pancreatic malignancy.

For comparison, there were no reports of DVT, or pulmonary embolism for that matter, in the risperidone or olanzepine premarketing NDA clinical trial databases. These cases raise the possibility of thrombophilic effects from quetiapine, although a few cases involving events that have a non-negligible expected rate are obviously not conclusive. It is perhaps relevant that a chemically similar compound, clozapine, may be associated with an increased risk of pulmonary embolism.

If these cases do, in fact, represent a true association of quetiapine treatment with thrombotic events, there may be a biologically plausible mechanism. Hughe's syndrome, also known as the antiphospholipid antibody syndrome, is a well described immune phenomenon involving circulating antiphospholipid antibodies. These antiphospholipid antibodies may include anticardiolipin antibodies or the lupus anticoagulant, the latter so called because it was first described in association with lupus erythematosus and because it results in a paradoxical elevation of the partial thromboplastin time. Presence of these factors has been linked to increased risk of venous or arterial thromboembolic events and to recurrent fetal loss. While often associated with autoimmune disease, presence of these antibodies has also been linked to treatment with neuroleptic drugs such as chlorpromazine, although the clinical significance is uncertain (Mueh et al., Ann Intern Med 1980; 92:156-159; Lillicrap et al, Am J Clin Pathol 1990;93:771-775). (As there are now routine serum assays for these antibodies, it should be feasible to test the possibility of an association of quetiapine treatment with antiphospholipid antibodies.)

8.2.1.3 Adverse cardiovascular events considered unlikely to be quetiapine related

As shown in appendix table 8.1.1.1, quetiapine patient 0012OLE/0045/4502 died from cardiovascular causes that did not appear related to quetiapine therapy (cardiopulmonary arrest following worsening angina). In addition, two subjects in study 0048 were reported to have died from cardiac disease after the NDA cutoff date, one from a myocardial infarctionand one from possible cardiopulmonary arrest, but only incomplete information is available at this time.

The following were nonfatal but clinically significant adverse cardiovascular events, deemed

unlikely to be related to quetiapine.

0031/0009/0903
42 year old man with chest pain, tachycardia; MI was ruled out

0048/0002/0201
70 year old man with congestiveheart failure; also chronic obstructive pulmonary disease anemia and acute renal failure

0048/0018/1811
70 year old man with new onset (presumably) of atrial fibrillation accompanied by chest pain

0012 OLE/0019/1904
52 year old male with ischemic heart disease was hospitalized for chest pain

0017 OLE/0001/0102
63 year old diabetic male suffered acute myodardial infarction

0061/0001/0107
45 year old man hospitalized for angina pectoris, underwent angioplasty

0035/0001/0132
Phase 1 study. 30 year old male with history of intravenous drug abuse. Subacute bacterial endocarditis with renal embolus.

0014/0016/1605
47 year old male hospitalized with diagnosis of poor cerebral perfusion secondary to mitral and aortic valve lesions

0017/0002/0202
66 year old male hospitalized with unstable angina

Trial H-15-33 Subject B
A 24 year old volunteer receiving quetiapine 10 mg/d in a phase I study had 18 beats of ventricular tachycardia, without symptoms, noted on holter monitoring

8.2.2 Gastrointestinal

8.2.2.1 Adequacy of assessment of gastrointestinal (GI) system effects

In the clinical development program, adverse GI events were collected by spontaneous report, and standard clinical laboratories were obtained. In my opnion, this was adequate assessment of the GI system. At the level of individual cases, however, the sponsor did not always obtain adequate followup information for patients discontinuing because of GI adverse events.

8.2.2.2 GI adverse events considered possibly, probably, or definitely related to quetiapine

Increased liver enzymes

In the pool of placebo controlled short term trials, 6% of quetiapine treated patients had ALT during treament of greater than or equal to 165 U/l, compared to 1.5% of placebo patients (p=0.0051). Group mean changes from baseline at end of treatment did not show very great disparaties between quetiapine and placebo for liver enzymes, however. Increased AST and ALT were among the more common reasons for premature discontinuations among quetiapine patients, although not occurring at a greater incidence than for control group patients (see tables in section 8.1.3.2 above). Increased ALT was a common and drug related adverse event, as

noted above in section 8.1.5.4.

I found no reference to specific criteria for withdrawal of patients having liver enzyme elevations, and it appears that this judgement was left to the investigators. Nonetheless, it may be useful to review the cases in which liver enzyme abnormalities resulted in dropout. The following table presents a summary of individual patients who discontinued quetiapine for liver enzyme elevation, based on the sponsor's case summaries.

Dropouts for liver enzyme elevations

Trial/subject	Age/ sex	Dose/duration	Maximum levels (IU/L)	Outcome/comments
5077IL/0005, Subject US-0001/0003	29 m	250 mg 22 d	ALT 267 AST 79	Returned to near normal roughly 2 weeks after d/c
H-15-22, Subject 27-2	22 m	300 mg 21 d	ALT 309; AST 104; ALK Ph 290; GGT 110	Returned to near normal roughly 2 weeks after d/c. Received unspecified agent for treatment of liver
H-15-22, Subject 45-1	43 f	450 mg 34 d	ALT 151; AST 116; Alk Ph 287; GGT 54	Returned to normal after d/c
H-15-22, Subject 62-2	33 f	300 mg 14 d	AST 103 ALT 206	Returned to normal 14 days after d/c
H-15-23, Subject 004/4-3	52 f	225 mg 101 d	AST 113 ALT 105	Concomitant carbamazepine. Liver treated with ursodesoxycholic acid, protoporphyrin disodium, liver hydrolysate, and glycyron. Continued slight elevationafter d/c
H-15-22, Subject 18-2	45 m	225 mg 15 d	AST 397 ALT 529	subject was treated with GLUTATHION 150 mg/day and protoporphyrin disodium 60 mg/day, VITANEURIN 3 capsules/day, SAIREITO (chinese medicine) 7.5 mg. Normal levels 6 weeks after d/c
H-15-22, Subject 27-2	22 m	300 mg 21 d also chlorpromazine	ALT 309 AST 104 Alk Ph 290 GGT 110	Receivied unspecified compound to treat liver. Near normal values 15 days after d/c
H-15-22, Subject 45-1	43 f	450 mg 34 d	SGOT: 116 , SGPT: 151, Al-p: 287 , γ-GTP: 54	Returned to normal after d/c
H-15-22, Subject 62-2	33 f	300 mg 14 d	AST 103 ALT 206	Returned to normal 2 weeks after d/c
5077IL/0006, Subject US-0005/0502	29 m	400 mg 20 d	ALT 302 AST 123	Returned to normal 17 days after d/c

204636/0008, Subject UK-0001/0020	22 m	100 mg 20 d	ALT 252 AST 119 GGT 82	Returned to normal 8 days after d/c
204636/0007, UK-Subject 0026/0004	33 f	100 mg 34 d	Alk Ph 987; AST 158; ALT 403; GGT 332	No Follow Up Information
5077IL/0012, Subject UK-0001/0118	38 m	400 mg 14 d	Alk Ph 285; ALT 448; AST 132	Normal liver ultrasound Day 7. Only ALT obtained in follow up (normal)
5077IL/0012, Subject UK-0029/2909	62 f	450 mg 25 d	Alk Ph 759; ALT 134; AST 89	Non A Non B hepatitis positive; liver enzymes increased during treatment; no followup
5077IL/0012, Subject UK-0086/8603	23 m	450 mg 36 d	ALT 395; AST 149	Normal 12 days after d/c
5077IL/0005 OLE, Subject US 0022/0003	29 m	250 mg 22 d	ALT 267; AST 79	ALT normal 2 weeks after d/c
5077IL/0012 OLE, Subject 0078/7807	40 f	150 mg 15 d	AST 123; ALT 258; Alk Ph 376	No follow up
5077IL/0012 OLE, Subject 0084/8402	29 m	250 mg 7 d	ALT 244	ALT actually decreased on treatment but investigator withdrew patient; no follow up

Note that in 4 cases no followup information was provided. For the other 14 cases, followup information indicated improvement after discontinuation of quetiapine. No patients were symptomatic. I am not aware of any patient discontinued for liver enzyme elevation who was later rechallenged with quetiapine.

The sponsor notes that of 21 quetiapine patients in short term controlled trials with treatment emergent ALT levels 3 times the upper limit of normal, 17 recovered without discontinuation of quetiapine.

In sum, elevation of ALT was associated at a statistically significant level with quetiapine treatment, relative to placebo, in short termstudies. No cases of hepatitis or other clinical manifestations of hepatic dysfunction, other than liver enzyme increases, have been observed with quetiapine treatment. Nonetheless, it cannot be known whether liver enzyme monitoring during the clinical trial program prevented some cases of more severe hepatic disorder, by prompting discontinuation of treatment when liver enzyme abnormalities occurred.

Dyspepsia and abdominal pain

In the pool of short term placebo controlled trials, treatment emergent abdominal pain was observed in more quetiapine than placebo patients by a statistically significant margin, and dyspepsia met the definition for common and drug related. These findings suggest some association of gastrointestinal distress with quetiapine therapy. Dyspepsia and abdominal pain were among the adverse events to have a statistically significant association with dose in the fixed dose controlled study 0013.

One adverse event involving GI distress met criteria fo r seriousness: A 23 year old male had to discontinue quetiapine for vomiting, anemia and weight loss of 9.5 kg, and required hospitalization (5077IL/0012 OLE, Subject 0002/0203). Also, subject 0014OLE/0026/2602, a 42 year old male, withdrew from quetiapine treatment after 183 days because of severe vomiting which had resulted in weight loss of 10 kg and malnutrition. This same patient had been hospitalized at week 6 for pancreatitis, but it appears from the sponsor'snarrative summary that the later episode of vomiting was not due to a recurrence of pancreatitis.

Dry mouth

The adverse event dry mouth, in the short term placebo controlled trials, was statistically significantly more frequent among quetiapine patients than placebo patients. Dry mouth also met the criteria for common and drug related.

8.2.2.3 Adverse GI events considered unlikely to be quetiapine related

The following lists patients that developed surgical problems while receiving quetiapine.

Trial and subject	Event and comments
5077IL/0031, Subject US-0006/0609	49 year old man (blind not broken) underwent surgery for a sigmoid volvulus
5077IL/0015, Subject US-0034/3407	39 year old female; laparotomy for a ruptured appendix
5077IL/0015 Subject US-0034/3408	27 year old male, surgery for appendicitis
0012 OLE/0032/3201	23 year old male; surgery for appendicitis
0014 OLE subject 0014/1402	surgery for suspected appendicitis; no outcome reported
0015/US -0005/0502	63 year old female developed intestinal obstruction attributed to post-surgical adhesions
0048 Subject US-0005/0502	small bowel obstruction attributed to post surgical adhesions in a 66 year old man; this resolved without surgery or discontinuation of quetiapine
5077IL/0048, Subject US-0001/0101	Stomach carcinoma in an 87 year old male
5077IL/0012, Subject UK-0003/0306	62 year old female with metastatic adenocarcinoma of the bowel

The following patients had non-surgical serious events related to the GI system.

5077IL/0017 OLE, Subject US-0004/0401	85 year old male hospitalized for severe constipation with impaction
5077IL/0012 OLE, Subject 0034/3402	42 year old male hospitalized for diarrhea; resolved without discontinuation of quetiapine.
0014 OLE/0026/2602	42 year old male hospitalized for pancreatits after 6 weeks of quetiapine treatment; recovered without discontinuation of quetiapine. (Patient later discontinued quetiapine for vomiting, at week 26 of treatment.)
5077IL/0012 OLE, Subject 0019/1903	35 year od male hospitalized for vomiting, but this resolved while quetiapine was continued
5077IL/0048 Subject US-0001/0104	91 year old female, hematemesis of unknown etiology

0048/US-0016/1612	75 year old man hospitalized for evaluation of abdominal pain. No etiology found, patient continued quetiapine therapy.
5077IL/0016, Subject 0001/0054 phase I	36 year old female diagnosed with hepatitis C
5077IL/0012 OLE, Subject 0086/8605	Elevated liver enzymes, ultimately deemed a lab error

8.2.3 Hemic and Lymphatic

8.2.3.1 Adequacy of assessment of Hemic and Lymphatic effects

Complete blood counts were monitored during every phase II-III quetiapine trial. In my opinion, this level of monitoring was adeqate. In addition, Zeneca submitted a report from Dr. Stanton Gerson, of the Hematology/Oncology division at Case Western Reserve University, on the hematologic findings associated with quetiapine treatment. One weakness in the clinical development program was the lack of follow up for patients with documented neutropenia, to ensure that their WBCs returned to normal after discontinuation of quetiapine. In a number of cases, as will be seen, no follow up was obtained after the patient had discontinued quetiapine for leukopenia.

8.2.3.2 Hemic and Lymphatic Adverse events Considered Possibly, probably, or Definitely Related to Quetiapine

(In this section, units for blood counts are 10^9/l.)

Leukopenia/neutropenia

In the pool of short term placebo controlled trials, examination of mean changes from baseline for white blood ceel (WBC) and absolute neutrophil count (ANC) reveals only modest changes associated with quetiapine (see appendix tables). Likewise, the number of patients having clinically significant changes in these counts was not significantly different compared to placebo. From the long term study 0015, the sponsor reports 7 out of 235 quetiapine treated patients, and 2 out of 40 haloperidol patients had ANCs below 1.5; however, one of these haloperidol patients had a baseline ANC below 1.5. Excluding that patient, the incidence of treatment emergent ANC below 1.5 was 3.0% for quetiapine patients and 2.6% for haloperidol patients.

Dr. Gerson provided an analysis of ANC and WBC values across the complete primary integrated database. The table below is adapted from his report submitted by Zeneca.

Numbers of patients with specific hematologic findings at any time during treatment [n (%)]

Finding (units =10^9/l)	Quetiapine (n=2387)	Placebo (n=206)	Active control (n=420)
Agranulocytosis (ANC < 0.5 and infection)	0	0	0
Severe neutropenia (ANC <0.5, no infection)	4 (0.2)	0	0
Moderate neutropenia (ANC ≥0.5 and <1.0)	19 (0.8)	1 (0.5)	1 (0.2)
Mild neutropenia (ANC ≥1.0 and <1.5)	65 (2.8)	3 (1.5)	6 (1.4)
Any Neutropenia (ANC <1.5)	88 (3.7)	4 (1.9)	7 (1.7)
Severe Leukopenia (<3.0 WBC))	42 (1.8)	0	2 (0.5)

There were proportionately more quetiapine patients in each of these categories, except agranulocytosis for which there were none; however, absolute incidence analysis is biased towards the quetiapine patient group which had a disproportionately longer exposure (due to open label extension treatments) and thus more time under observation to develop one of these findings. To examine this further, it is possible to calculate the incidence of neturopenia in terms of person time of exposure. For this, I have counted all patients who had an on-treatment ANC below 1.0 (10^9/l). The results are shown in the following table.

TABLE Neutropenia in the integrated Phase II-III clinical program

Treatment group	Number of subjects	Subject-years exposure*	Cases of neutropenia**	Crude incidence rate (%)	Incidence per 100 subject-years
Quetiapine	2387	865.3	23	0.96	2.7
Haloperidol and Chlorpromazine	420	51.7	1	0.24	1.9
Placebo	206	14.6	1	0.49	6.8

*Subject-years is defined as the sum of all subjects' days on treatment (duration) divided by 365 days.
** Combining agranulocytosis (no cases), severe neturopenia and moderate neutropenia

Of most concern clinically are patients who developed ANCs below 0.5x10^9/l. These patients are summarized below. Units are 10^9/l. No patients had symptoms related to their neutropenia reported.

Trial/subject	Comments
0006/0008/0814	33 y.o. male; ANC=0.28 and WBC 2.8 at week 2; repeat CBC the following day at another lab showed ANC=3.3 and WBC=7.4. Continued quetiapine and ANC returned to 1.96 at week 4.
0005/0017/0002	29 y.o. male; ANC=0.51 and 0.48, weeks 3 and 4 respectively; discontinued as lost to follow up after week 4 but later seen alive and well. [At week 2, patient's ANC was higher than total WBC, which is inconsistent. Also, the neutropenia was documented only at Zeneca's central laboratory; WBC and ANC from the investigator's local laboratory were normal:]

0012/0045/4508	36 y.o. male; ANC=0.43 at week 6, returned to 2.0 one week later without discontinuation of quetiapine
0012/0011/1106	34 y. o. male; ANC=0.27 at week 3, returned to 2.5 the following week with continuing quetiapine treatment

In three of the above cases, the neutropenia resolved while quetiapine was continued, and in one case the fact that the ANC was normal the next day by a different clinical laboratory casts doubt on the validity of the laboratory result. Resolution of neutropenia while the potentially offending drug is continued argues against a causal relationship, but does not rule it out completely (CIOMS report on Drug-induced cytopenia, Int J Clin Pharmacol Ther Toxicol 29:75-81,1991). The fourth patient's findings may have been a laboratory error and would be explained if someone mistook percent neutrophils for absolute neutrophils; i.e., if 0.51 was the proportion of neutrophils and not the absolute neurtrophil count.

The sponsor provided case summaries, prepared by their consultant, Dr. Gerson, of all individual cases of neutropenia with quetiapine treatment . This summary is reproduced in appendix 8.2.3.2. Note that Dr. Gerson considered 6 cases of neutropenia (0007/0017/0002, 0007/0017/0003, 0015/0018/1815, 0005/0018/0001, 0013/0007/0711, and 0014/0001/0103) as likely to be causally related to quetiapine treatment, based on clinical factors such as persistence and positive dechallenge. I find no reason to dispute his assessment.

A total of 14 quetiapine patients were withdrawn for the adverse event of leukopenia. However, there was no specific criterion for discontinuing patients based upon WBC, and in fact 3 patients with ANC below 0.5 were continued on quetiapine (and the fourth was lost to follow-up). In my opinion, because of these inconsistencies in withdrawing patients due to leukopenia, further analysis of dropouts for this adverse event is not likely to be informative.

Three patients were hospitalized for neutropenia during quetiapine treatment; however, no symptoms were reported. Patient 0012OLE/0064/6406, a 33 year old man, was hospitalized when his ANC fell to 1.3. Two days after quetiapine was discontinued his ANC returned to 3.5. Patient 0014OLE/0045/4506, a 24 year old female, was hospitalized when her WBC dropped to 2.5 with an ANC of 1.1; her counts improved after quetiapine discontinuation. Patient 0012OLE/0005/0506 was hospitalized for an ANC of 1.1; the count returned to normal after quetiapine was discontinued. As with dropouts for decreased WBC, there were no specific clinical criteria that lead to these particular patients being hospitalized, other than clinical judgement; and other patients with more severe decreases in WBC were not hospitalized.

The Division sought consultation on the question of quetiapine associated leukopenia from the Division of Gastrointestinal and Coagulation Drug Products. Please refer to the consultation by Dr. Lilia Talarico. She concluded that certain instances of quetiapine associated neutropenia were causally related to administration of the drug, but that these were apparently benign. She based this judgement on the pattern of decline in WBC following quetiapine treatment in certain cases and the fact that recovery often occurred after the drug was discontinued. Additionally, she observed that for the total primary integrated safety database, the incidence of neutropenia was slightly increased in the quetiapine patient group compared to the control groups.

In sum, quetiapine treatment was not prominently associated with neutropenia relative to the active control or placebo treatments. However, both the sponsor's consultant, Dr. Gershon, and Dr. Talarico from the FDA Division of Gastrointestinal and Coagulant Drug Products felt that quetiapine treatment induced leukopenia and neutropenia in certain individual patients. No

cases are known to have progressed to agranulocytosis. What cannot be known, of course, is to what extent the WBC monitoring which resulted in discontinuation of a number of patients from quetiapine treatment prevented more serious cases of neutropenia.

Thrombocytopenia

In her consultation report, Dr. Talarico commented upon the fact that a number of quetiapine treated patients had thrombocytopenia of a significant degree (less than 75K/uL). She notes that one of these patients had simultaneous leukopenia (paitent 0048/0010/1014). Review of this patient's laboratory data revealed that on the day following the result showing thrombocytopenia and leukopenia, the CBC had returned to normal, casting doubt on the clinical significance. (Dr. Talarico also noted in her consult that patient 0015/0005/0502 had not only thrombocytopenia but pancytopenia; however, the most persistent abnormality for this patient was anemia, and so the patient is listed below in the section on anemia.)

With the CANDA data review funtion, patients with thrombocytopenia were identified and their platelet count data were examined individually. A total of 11 patients had platelet counts below 75K while recieving quetiapine; however, in all but two cases these were isolated low values which resolved with continued quetiapine exposure. In the remaining two cases which involved more persistent low platelet counts (patients 0014/0033/3307 and 0048/0002/0208) the baseline platelet counts were also low (57K and 78K, respectively). Thus there does not seem to be a strong signal for drug induced thrombocytopenia from these data.

Anemia

Aggregate data from the short term controlled trials, as shown in the appendices, suggested mean decreases in hematocrit with quetiapine, but no corresponding decrease in hemoglobin. However, in her hematology consultation report, Dr. Talarico noted that a number of quetiapine treated patients had a significant degree of anemia (Hgb less than 10 g/dl). To investigate this further, an electronic search of the CANDA primary integrated database (data set 4msudbol) was conducted, using the JMP statistical application, for patients whose minimum Hgb on treatment was less than 10 g/dl. This yielded 19 such patients; however, 4 had baseline Hgb below 10 g/dl as well. Excluding these patients, there were 14 quetiapine and 1 chlorpromazine patients with treatment emergent Hgb less than 10 g/dl. The individual patient data for the quetiapine patients was reviewed. In the majority of these cases the anemia resolved while quetiapine was continued, although one patient (0012/0092/9207) was noted to have received unspecified treatment for the anemia. A few of these cases, however, involved anemia that was not transient and are described in the table below:

Selected cases of treatment emergent anemia (Hgb < 10 g/dl) with quetiapine

Trial/patient number	Comments
0013/0016/1605	43 y.o. female with anemia and deep vein thrombophlebitis (DVT), discontinued for lack of efficacy
0015/0005/0502	63 year old female with multiple serious adverse events described elswhere (sepsis, bowel obstruction, DVT); also had anemia (Hgb nadir =6.4 g/dl) without an etiology reported. Thrombocytopenia, neutropenia, and eosinophilia were also documented but did not persist as long as the anemia. The final on-treatment CBC was normal.
0048/0004/0405	81 year old male patient had Hgb less than 10 g/dl on several occassions while receiving quetiapine; anemia not recorded as adverse event

0014ole/0046/4609	51 year old male, mild anemia pretreatment (Hgb 13.7 g/dl), hospitalized for severe anemia after 135 days of quetiapine treatment. The lowest hgb recorded was 8.6; hgb improved after quetiapine was discontinued.
0048/0002/0201	70 year old man with congestive heart failure, hospitalized with acute renal failure attributed to concomitant trimethoprim-sulfa by sponsor. (This event will also be noted under the Genitourinary system.); simultaneously had profound anemia (hct 20), with total bilirubin of 8.6 umol/l . Little additional information was available

One other patient had anemia that became a serious adverse event: Patient **0012OLE/0002/0203** was hospitalized with weight loss, vomiting and anemia (Hgb 10.2); according to the case report form the anemia was attributed to vomiting and the patient also had an esophageal ulceration. The vomiting, however, was not described as hematemesis (which could have accounted for a drop in hemoglobin).

Little additional information relating to anemia was available for these cases. At the time of writing this review, the sponsor had been asked to provide additional clinical information regarding some of the above patients. With the limited information available at present, it is not possible to rule out a drug related cause (e.g., hemolysis).

Eosinophilia

In study **5077IL/0014 OLE, Subject 0026/2608**, a 38 year old female, was withdrawn for eosinophilia after 3 weeks of quetiapine treatment, with eosinophil count increased from a baseline of 0.2 to 2.0 (with WBC 11.4); no follow up counts were obtained. The patient also had an episode of bronchitis. Eosinophilia is often an adverse drug reaction.

8.2.3.3 Adverse Hemic and Lymphatic events considered unlikely to be related to quetiapine

There were none.

8.2.4 Metabolic and Endocrine

8.2.4.1 Adequacy of assessment of metabolic and endocrine effects

Body weight was assessed regularly during the quetiapine clinical trials. With respect to clinical laboratories, cholesterol and triglyceride levels were obtained in certain of the domestic studies, although these were not required to be fasting samples. Some type of thryoid hormone monitoring was performed in 11 phase II-III trials, although the specific tests obtained varied from study to study. Prolactin was measured in the majority of phase II-III clinical trials. Of particular interest with respect to hormonal measurements is the data from the one year dose comparison long term treatment trial, study 0015, which provides some data on long term effects. On balance, this body system received an adequate evaluation during the quetiapine clinical trials, in my opnion.

8.2.4.2 Metabolic and Endocrine System Adverse events Considered Possibly, probably, or Definitely Related to Quetiapine

Hypothyroidism

In animals, the sponsor reports that quetiapine enhances hepatic clearance of thyroxine, resulting in elevated TSH, which in turn leads to thyroid follicular cell hypertrophy and benign thyroid tumors. Additionally, thyroid glands in rats exposed to quetiapine chronically contained pigment granules of drug derived substance.

Analyses of central tendency for thyroid function

In the pool of short term, placebo controlled trials, quetiapine treatment was associated with mean decreases in total T4 and free T4 of around 20%, but was not associated with an increase mean TSH levels. Complete data is shown in appendix table 8.1.6.3.1b.

It may be instructive to consider the thyroid function test data from the one year relapse prevention study, trial 0015. The following is an adaptation of a table from the sponsor's study report.

TABLE Mean change from baseline to final evaluation for thyroid function tests, study 0015 (adapted from sponsor's study report)

Parameter	Treatment Group: Quetiapine 75 mg n	75 mg mean$_\Delta$ (SD)	Quetiapine 300 mg n	300 mg mean$_\Delta$ (SD)	Quetiapine 600 mg n	600 mg mean$_\Delta$ (SD)	Haloperidol n	Haloperidol mean$_\Delta$ (SD)
Total T_4 (nmol/L) (57.9 to 160.9 nmol/L)	69	0.52 (18.6)	73	-12.16 (22.0)	69	-24.02 (24.5)	36	0.86 (24.2)
Free T_4 (pmol/L) (15.4 to 29.6 pmol/L)	69	-0.88 (3.8)	73	-1.50 (4.2)	69	-3.25 (3.0)	38	0.68 (4.5)
Total T_3 (nmol/L) (1.3 to 2.8 nmol/L)	68	-0.05 (0.4)	72	-0.08 (0.4)	69	-0.19 (0.4)	36	-0.04 (0.4)
Reverse T_3 (nmol/L) (0.04 to 0.29 nmol/L)	50	-0.01 (0.1)	62	-0.01 (0.1)	56	-0.03 (0.1)	32	0.01 (0.1)
TSH (µU/L) (0.4 to 5.5 µU/L)	69	-0.16 (0.9)	73	0.03 (1.1)	69	-0.13 (1.3)	38	-0.14 (0.8)
TBG (nmol/L) (20592 to 43758 nmol/L)	52	-1114 (5490)	63	-1471 (5132)	59	-1112 (6397)	32	1086 (4905)

SD Standard deviation

It can be seen that the pattern of reduction in thyroxine, both free and total, is dose related. Examination of the mean changes for thyroxine levels in this study by week showed that after an initial decrease at the four week visit, mean values remained fairly constant in each group, suggesting that the decreases were not progressive over time.

Note that in both the short term and the long term trials, only minor variations in mean TSH levels are seen.

In the fixed dose study 0013, mean decreases in total thyroxine were statistically significant compared to placebo, and also followed a dose related pattern.

Analysis of outliers for thyroid function tests

A statistically significant number of quetiapine patients in short term placebo controlled trials had

treatment emergent decreased total T4, defined as a level more than 20% below the lower normal limit, compared to placebo (see appendix table 8.1.6.3.2b).

In the report to the U.K., the sponsor noted the results of a search of the Phase II-III trials (incliuding safety update) for patients who had clinically significant TSH elevation, defined as a persistent treatment emergent TSH elevation or one that resulted in prescription of thyroid replacement therapy. There were 11 such quetiapine patients, although one had a recent history of lithium induced hypothyroidism and was excluded from the total. This left a total of 10 such patients (incidence of 0.4%, or 1.2 per 100 patient years), compared to 0/420 active control patients (with 51.7 patient years) and 0/206 placebo patients (with 14.6 patient years). Of the ten patients, 6 were prescribed thyroid hormone replacement.

Other data

A total of 13 quetiapine patients in the primary integrated database had hypothyroidism reported as an adverse event; no patients from the control groups had this event. In all cases the diagnosis was based on laboratory rather than clinical. findings. It should be remembered, however, that the clinical diagnosis of incipient hypothyroidism can be subtle, relying as it does on symptoms such as lethargy and weight gain which might be particularly difficult to detect in a chronically mentally ill population. In one case (5077IL/0031 OLE, Subject US-0008/0801), hypothyroidism was a serious event. This patient, a 33 year old man, had a progressive increase in his TSH level, beginning during double blind treatment (blind not yet broken) and continuing during open label quetiapine treatment. He was hospitalized for evaluation after his TSH and T_4 levels reached 66.5 mIU/L and 0.8 ng/dl, respectively. He responded to treatment with levothyroxine and continued quetiapine therapy.

The sponsor's report to the U.K. CSM indicates that treatment emergent reduction in free T4 has been observed in quetiapine treated patients with pre-existing hypothyroidism receiving concomitant L-thyroxine, but without an accompanying increase in TSH. No specific data were provided to support this observation.

Because of the histopathology findings in rats exposed to quetiapine chronically, the available autopsy reports for patients who expired during clinical trials were reviewed for evidence of histologic changes in the thyroid. Patient 0048/0007/0703, a 92 year old male who died of respiratory related causes after receiving quetiapine for 191 days, at autopsy had a thyroid gland with a nodular goiter and a microscopic papillary carcinoma. Patient 0014/0043/4304, who died suddenly while receiving haloperidol in a clinical trial, at autopsy had a small papillary carcinoma of the thyroid. Patient 0031/0021/2104, who drowned while receiving treatment that is still blinded, at autopsy had an enlarged thyroid with a cystic mass in the left lobe. No other autopsy reports mentioning the thyroid were available (only a summary report was available for patient 0012/0091/9103). With so few cases, inferences are not possible regarding histologic findings in the thyroid gland.

Zeneca has proposed that the pattern of thyroid function test findings for quetiapine is similar to those found with phenytoin and carbamazepine, and thus of no great clinical consequence. Recently it has been proposed that the observed decrease in free T4 and T3 in patients receiving these anticonvulsant drugs is actuallya laboratory artifact. The usual assay for these hormones involves dilution of the serum prior to measurement of the free hormone levels. Surks and DeFesi (JAMA 1996;275:1495-1498) determined that free hormone levels in patients receiving these drugs where normal when measured without dilution of the serum, but were low when the serum was diluted for the standard assay technique. Their conclusion was that in undiluted

serum the drugs competitively displace thyroid hormones from binding proteins; when the samples are diluted in vitro the equilibrium is altered, displacement is reduced and the result is underestimated free hormone levels. In fact, one of Zeneca's consultants (Dr. Toft, 4/14/97 submission) suggested assaying free T4 with a different technique (i.e., the Amerlite-MAb technique); I am not aware that Zeneca has done so.

Consultation was requested from the Division of Metabolism and Endocrine Drug Products regarding the thyroid hormone abnormalities observed with quetiapine. Dr. Jean Temeck responded to the consult; please refer to her review dated 5/29/97. For her review, the sponsor made a special submission of individual patient data (3/27/97). Additionally, the sponsor provided a review of thyroid data including reports from two consultants, prepared for the U.K. Committee on Safety of Medicines (4/14/97). Dr. Temeck concluded that quetiapine was associated with decreased total T4 (TT4) and free T4 (FT4), not accounted for by concomitant drugs that might have affected thyroid function (e.g., lithium). These changes were dose related. She indicates that the observation that the majority of changes in TT4 and FT4 were not accompanied by increased TSH is consistent with a peripheral mechanism. Dr. Temeck noted that it might be reasonable to monitor thyroid function in patients receiving quetiapine who are at risk for hypothyroidism (either by virtue of past history of hypothyroidism, or a family history).

In summary, quetiapine treatment is associated with decreased thyroxine (both free and total) in a dose dependent manner. The decreases are rarely associated with an increase in TSH and infrequently associated with frank clinical hypothyroidism. The clinical significance of these abnormalities is therefor uncertain. The mechanism is unknown but it is possible that it is related to the assay method employed.

Weight Gain

In short term placebo controlled trials, roughly 23% of quetiapine patients experienced clinically significant weight gain (increase of 7% or more), compared to approximately 6% of placebo patients, a statistically significant difference. In these trials, quetiapine patients had a mean weight gain of 2.3 kg at the end of treatment compared to 0.1 kg for placebo. Complete data is displayed in appendix tables 8.1.7.3.1 and 8.1.7.3.2. In the short term fixed dose study 0013, and the long term fixed dose study 0015, weight gain reported as an adverse event showed a statistically significant relationship to dose. There was only one patient receiving quetiapine who discontinued with weight gain (as a contributing factor to withdrawal, along with somnolence and abdominal distension): in trial **5077IL/0012, Subject UK-0007/0708**, a 37 year old female.

Cholesterol and triglycerides

Plasma triglyceride and cholesterol levels were obtained in certain of the placebo controlled trials, but these were not necessarily fasting levels. Expressed as percent change from baseline, the results show a mean increase from baseline of 11% for cholesterol and 17% for triglycerides with quetiapine treatment, without similar increases in the placebo group. These data are displayed in appendix table 8.1.6.3.1b.

In dogs and monkeys, quetiapine was associated with a decrease in cholesterol levels, attributed to inhibition of cholesterol biosynthesis. In humans, the data are more consistent with an increase in cholesterol, although fasting blood concentration data would be more reliable. It should be recalled that increased cholesterol concentrations are associated with clinical hypothyroidism. Cardiovascular risk is believed to be related to cholesterol levels in a continous manner; i.e., there is no threshold for the increase in risk associated with an increase in serum

cholesterol.

Prolactin

Hyperprolactinemia is commonly associated with neuroleptic treatment and is attributed to dopamine blockade in the hypothalamus. In the quetiapine animal chronic toxicity studies, prolactin concentrations were elevated in rats and in male monkeys, but not in female monkeys or dogs. The only patient in the primary integrated database to have prolactin increase reported as an adverse event was receiving chlorpromazine. No patients withdrew because of hyperprolactinemia. In the quetiapine short term placebo controlled trials, mean prolactin concentrations for quetiapine subjects actually decreased, as they did with placebo. No quetiapine patients in this pool of placebo controlled clinical trials had a prolactin concentration above the criterion value of 100 ug/l., although 3.1% of quetiapine patients had a shift in prolactin concentration from normal to high with treatment compared to 1.6% of placebo patients. Study 0013 affords an opportunity to assess the change in prolactin concentrations by quetiapine dose, with placebo and haloperidol as comparison treatments. The table below displays prolactin data from study 0013.

TABLE **Analysis of covariance of change from baseline in prolactin concentrations (mg/L) at final evaluation, Study 0013 (adapted from sponsor's study report)**

	Treatment group						
	Quetiapine					Haloperidol	Placebo
	75 mg (n = 19)	150 mg (n = 25)	300 mg (n = 31)	600 mg (n = 28)	750 mg (n = 28)	12 mg (n = 24)	(n = 19)
Baseline mean	10.00	17.12	12.03	9.93	17.25	9.50	11.84
LS mean change (SE)	-0.51 (2.85)	-2.10 (2.50)	-0.21 (2.23)	-0.76 (2.35)	-1.93 (2.36)	18.30* (2.54)	1.99 (2.84)

*Significantly different from placebo group
LS = least squares SE = standard error

In the data shown above from study 0013 there was an increase in prolactin concentrations for the haloperidol group but not for any quetiapine group. It may be that the decreases from baseline that were observed reflected prolactin elevation at baseline arising from the patient's previous neuroleptic therapy. With the aid of the Seroquel CANDA date review function (trial 0013 data set n_prolac, imported to JMP statistical application), I was able to subset the prolactin data from this study by sex, and there did not appear to be significant sex differences in the mean changes from baseline to endpoint. This is in contrast to the animal data noted above.

In the active controlled study 0007, mean prolactin concentrations did not increase for the chlorpromazine group or the quetiapine group, although this would have been expected for the chlorpromazine group at least.

On balance, quetiapine treatment does not appear to have a very robust effect on plasma prolactin concentrations, from these clinical data. Conceivably, however, a modest effect on prolactin could be obscured because many of the patients in the clinical trials were previously receiving dopamine blocking drugs.

Neuroleptic Malignant Syndrome

Two patient receiving quetiapine had episodes consistent with neuroleptic malignant syndrome (NMS), a hypermetabolic drug induced state associated with neuroleptic use. These two cases are summarized below.

Table Summary of possible NMS cases with quetiapine

Trial;subject	age	sex	quetiapine dose (mg) and duration	concomitant drugs	comments
5077IL/0012, UK-0049/4903	33	f	50 mg/d X 4 d	levothyroxine	Ridigidy, unresponsiveness, drooling, tachypnea, tachycardia, creatine kinase (ck) peaked at 1131 iu/l. Recovered after intensive care admission with dantrolene, bromocriptine and phenytoin therapy. Dx was NMS versus catatonia.
5077IL/0015, US-0009/0901	36	m	300 mg/d maximum x 13 d	benztropine	Altered mental status, rigidity, catatonia, tachycardia to 131 bpm, leukocytosis, fever, CK=2050. Recovered after hospitalization; treated with haloperidol afterwards.

There were no similar cases among patients receiving control group therapies. In my judgement, it is reasonable to label these cases as possible NMS. These two cases represent an incidence of 8.4 per 10,000 patients exposed to quetiapine, or 2.3 per 1000 patient years of exposure.

8.2.4.3 Adverse metabolic and endocrine system events considered unlikely to be related to quetiapine

Three patients had serious adverse events involving glucose dysregulation:

Trial and Subject	Event and Comments
5077IL/0048, Subject US-0007/0706	hypoglycemia (Suspected inadvertent administration of hypoglycemic agent by staff at the subject's nursing home)
5077IL/0012 OLE, Subject 0093/9304	Hyperglycemia in a diabetic female
5077IL/0013 OLE, Subject 0001/0109	Hyperglycemia in a 44 y.o. male with past history of hyperglycemia

Three patients had serious adverse events involving electrolyte abnormalities:

5077IL/0048, Subject US-0007/0714	Dehydration in an elderly female with dementia
5077IL/0013 OLE, Subject US-0006/0613)	Hyponatremia and convulsion
5077IL/0013 OLE, Subject 0023/2312	Water intoxication

Polydipsia is a common problem among chronic schizophrenic patients.

8.2.5 Musculoskeletal

8.2.5.1 Adequacy of assessment of musculoskeletal system

No formal evaluations of the musculoskeletal system were incorporated in the clinical trials, to my knowledge, other than general physical examinations. However, I believe this was reasonable.

8.2.5.3 Adverse events considered related to quetiapine

Falls and Fractures

Three patients had fractures associated with postural hypotension or syncope (events discussed under Cardiovascular system). A 58 year old female fainted while on quetiapine and fractured an ankle (**5077IL/0012, Subject UK- 0005/0501**); similarly, a 46 year old female fractured a bone in her foot with a syncopal episode (**5077IL/0015 OLE, Subject 0019/1903**). A 58 year old female with treatment emergent postural hypotension fell and fractured her ankle (**5077IL/0012, Subject UK-0005/0501**). syncope is discussed under cardiovascular events.

Other such events, however, were not so clearly linked to orthostasis. An 89 year old woman fell and sustained an intertrochanterichip fracture; the cause was uncertain (**5077IL/0048, Subject 0006/0601**) but could have been drug related. Likewise, in study **5077IL/0048, Subject US-0007/0714**, a 74 year old woman with dementia, fell and lacerated her scalp with no clear precipitant. In study **5077IL/0015, Subject US-0030/3002**, a 65 year old man receiving quetiapine 75 mg/d, fell and hit his head on a sink sustaing head trauma and facial injuries requiring hospitalization. In study **5077IL/0012 OLE, Subject 0059/5907**, a 45 year old man, fell without an obvious cause and sustained oral and dental injuries and was discontinued from quetiapine.

Altogether, there were a total of 20 adverse events coded as pathological fracture in the primary integrated database; all occurred in quetiapine treated patients. Since hip fracture in the elderly can be a particularly significant injury, the electronic database was searched (data set adversev from trial category 4msudbol) to identify patients 65 years old and older who sustained hip fractures. There were a total of 4 such patients (**5077IL/0048, Subject 0006/0601**, **5077IL/0048, Subject US-0013/1303**, **5077IL/0048, Subject US-0002/0208**, **5077IL/0048, Subject US-0013/1307**). Ignoring for the moment the fact that some cases may not have been related to the drug (see below), and combining males and females, with 190 patients over 64 years old contributing 84.5 patient years in the quetiapine primary integrated database (calculated with CANDA electronic data set 4msudbol/ddemog), these cases represent an incidence of 2.1%, or 4.7 per 100 patient years, for hip fracture associated with quetiapine treatment. For reference, Weintraub and Handy (Clin Pharmacol Ther 1993; 54(3):252-6) reported data from New York State showing a rate of hip fracture in the general population aged 75 years and older of approximately 1.4 per 100 person years for women and 0.7 per 100 person years for men. While hip rracture is not rare in this age group, it is plausible that quetiapine's sedative and/or orthostatic effects may have contributed to falls among the elderly.

8.2.5.4 Adverse musculoskeletal events considered unlikely to be related to quetiapine

Trial/subject	Event and comments
5077IL/0048, Subject US-0013/1307	66 year old female; hip fracture after falling out of bed while hospitalized for evaluation after a seizure
5077IL/0048, Subject US-0013/1303	71 year old male with dementia; fell over his dog and fractured hip
5077IL/0048, Subject US-0002/0208	75 year old female with dementia fractured her femur; fall attributed to parkinson's disease

5077IL/0048, Subject US-0007/0713	**80 year old male attempted to climb out of hospital bed and fractured fibula**
5077IL/0013, Subject US-0026/2614	**30 year old male fractured malleolus during a fight**
5077IL/0015 OLE, Subject US-0026/2614	**65 year old male tripped and fractured his arm while boarding a bus**

In addition, one placebo patient in a Japanese trial sustained a femur fratcture with a syncopal episode (H-15-21, Subject 9-1).

8.2.6 Nervous

8.2.6.1 Adequacy of assessment of nervous system events

Adverse nervous system events were reported spontaneously in the usual manner. In addition, the sponsor employed the Simpson-Angus scale for measuring extrapyramidal sympotms (EPS), and the Abnormal Involuntary Movement Scale (AIMS) for assessment of dyskinesia. Zeneca also analyzed the use of anti-EPS medication during clinical trials. In my view, this was an adequate assesment of the nervous system.

8.2.6.2 Nervous System Adverse events Considered Possibly, probably, or Definitely Related to Quetiapine

Extrapyramidal symptoms (EPS)

The 6 week fixed dose placebo controlled trial 0013 affords an opportunity to examine dose response with respect to EPS. The table below presents the results from the Simpson EPS rating scale by dose group.

TABLE: Simpson scale: Mean change from baseline to final evaluation in total score, Trial 0013 (adapted from sponsor's ISS)

	Treatment group						
	Quetiapine					Haloperidol	Placebo
	75 n = 50	150 mg n = 46	300 mg n = 49	600 mg n = 49	750 mg n = 49	12 mg n = 49	n = 50
Baseline mean (SD)	12.8 (4.2)	12.8 (3.6)	13.0 (4.1)	13.4 (4.6)	13.4 (4.0)	12.6 (3.2)	12.9 (3.7)
Change from baseline mean (SD)	-1.0 (3.2)	-1.2 (2.7)	-1.6 (2.6)	-1.8 (3.6)	-1.8 (3.9)	1.1 (5.6)	-0.6 (3.3)

Note the absence of a dose effect. There was a slight mean worsening of scores for the haloperidol group. The sponsor also analyzed the use of anti-EPS medication (benztropine) during the study by dose group, as shown below.

TABLE Number of subjects receiving benztropine mesylate for EPS concurrently with quetiapine, haloperidol, or placebo in Trial 0013 (adapted from sponsor's ISS)

	Quetiapine					Haloperidol	Placebo
	75 mg (n = 53)	150 mg (n = 48)	300 mg (n = 52)	600 mg (n = 51)	750 mg (n = 54)	12 mg (n = 52)	(n = 51)
Number of subjects (%)	6 (11)	5 (10)	4 (8)	6 (12)	6 (11)	25 (48)	7 (14)

The most use of benztropine was among the haloperidol group. The number of quetiapine treated patients who used benztropine was similar across dose groups and was comparable to the placebo group.

EPS was not a common drug related adverse event in the short termplacebo controlled trials, nor was it among the adverse events most often accounting for withdrawals.

The adverse event dystonia showed a trend for a dose response ($p<0.10$) in the long term relapse prevention trial (0015).

Examination of the sponsor's compilation table of dropouts from quetiapine treatment reveals that for the primary integrated database (n=2387), the following numbers of patients discontinued for EPS adverse events: akathisia, 2; dystonia, 1; EPS unspecified, 1; hypokinesia, 1; movement disorder, 1. These numbers are taken from controlled and uncontrolled studies; Although precise comparisons to control groups are not possible due to the dirrefence in exposure duration, these cases represent relatively few of the adverse events leading to withdrawal in the primary integrated database.

One patient in a Japanese trial developed akathisia that was deemed a serious adverse event, while receiving quetiapine 75 mg/d (**H-15-22, Subject 6-1**). Another Japanese patient developed choreoathetoid movements which resolved after discontinuation of quetiapine (**H-15-22, Subject 47-1**).

In sum, quetiapine's propensity to induce EPS appears modest.

Tardive Dyskinesia

Tardive dyskinesia (TD) is a movement disorder that develops with chronic neuroleptic therapy; consequently, evaluation of the hazard associated with a new antipsychotic drug is difficult from a premarketing database that comprises a substantial proportion of short term exposure. Another complication results from the fact that many patients have a previous history of exposure to neuroleptics, making attribution to a particular drug difficult if TD is observed.

To evaluate tardive dyskinesia manifestations associated with quetiapine treatment the sponsor conducted AIMS assessments, as noted above. For tardive dyskinesia, it is most appropriate to consider long term treatment data; accordingly, the findings from the one year relapse prevention study are shown below.

TABLE Frequency distribution for change from baseline in AIMS total score at the final evaluation, Study 0015 (adapted from sponsor's study report)

	Treatment group			
	Quetiapine			Haloperidol
	75 mg n(%)	300 mg n(%)	600 mg n(%)	12 mg n(%)
Change from baseline				
-3 or less	12 (17)	12 (17)	13 (18)	5 (14)
-2 to -1	15 (22)	10 (14)	16 (23)	5 (14)
0	26 (38)	27 (38)	27 (38)	17 (46)
+1 to +2	4 (6)	6 (8)	10 (14)	1 (3)
+3 or greater	12 (17)	17 (24)	5 (7)	9 (24)
Total	69 (100)	72 (100)	71 (100)	37 (100)

Here, the pattern of changes in AIMS scores was fairly similar for all 3 doses and for haloperidol. However, haloperidol is a drug that is accepted to cause TD, so negative findings with quetiapine in this trial are not completely reassuring given the absence of a positive finding with haloperidol.

One patient (0015/0034/3404, a 47 year old man) discontinued quetiapine 600 mg daily because of treatment emergent TD which developed over several months. The patient had a history of TD with haloperidol, but had no manifestations of TD at the beginning of quetiapine treatment. In a similar case, patient 0027OLE/0001/0103 had worsening of buccolingual movements during quetiapine treatment. Also, a Japanese patient (H-15-23/010/11-6, a 61 year old woman) developed TD after 75 days on quetiapine (maximum dose 750 mg). This patient , although not naive to neuroleptics, did not have TD at baseline.

In sum, quetiapine treatment has been associated with TD in some patients. There is inadequate data from which to estimate a cumulative incidence at present. Assessment of this adverse drug reaction is further complicated by the fact that many patients had previous exposure to other neuroleptics.

Somnolence

In the pool of short term controlled studies, somnolence was a common and drug related adverse event, with an incidence of 17.5% for quetiapine compared to 10.7% for placebo (p=0.0005). Somnolence did not show a statistically significant dose response relationship in either the long term fixed dose study (0015) or the short term fixed dose study (0013). Somnolence was the most frequently reported adverse event leading to premature discontinuation (n=27 for the primaryintegrated database of 2387 quetiapine treated patients.) One patient, a 36 year old woman (0014/0053/5307), had to be hospitalized because of sedation but apparently recovered after a dosage reduction. Another patient (0012/UK0070/7006), a 21 year old man, had somnolence so severe on his first day of quetiapine treatment that he awoke only to painful stimuli; an EEG showed rapid activity consistent with a drug reaction, and he recovered within a few hours.

Convulsions

The table below summarizes patients who had one or more seizures while receiving quetiapine. The primary source for this list was the sponsor's patient narratives for serious adverse events; all convulsions were considered serious adverse experiences by the sponsor.

Table Summary of seizure (sz) cases with quetiapine treatment

Trial;subject	age	sex	quetiapine dose (mg) and duration	concomitant drugs	comments
0048/0013/1306*	64	f	≥50 d ≥200 mg	Carbamazepine Tenormin, iron	3 seizure episodes during trial
0048/0013/1307*	66	f	5 mo 150 mg	numerous	Tonic clonic sz; recent DVT
H-15-22, 58-4	40	m	8 d/75 mg		"severe seizure"
0033OLE-0002/0001*	34	m	5 d	clonazepam (dose recently reduced)	Sz attributed to clonazepam withdrawal
0048/ 0001/0109*	65	m	500 mg 29 wk		Patient with alzheimer's dementia
0048/0001/0115*	70	m	6 days after d/c quetiapine	chloral hydrate, lorazepam, haloperidol	Sz while hospitalized for CVA
0048/0006/0601*	89	f	75 mg 12 wk	numerous	Patient with dementia; treated with DPH and remained in study
0012/0005/0543*	23	f	800 mg 3 mo		Newly diagnosed with temporal lobe epilepsy
0012 OLE/0036/3604*	55	f	700 mg 19 mo		Diagnostic evaluation unrevealing
0031 OLE/0023/2302	39	m	600 mg d/c 2 days prior to sz	Lorazepam, thiothixene, clonazepam	3 tonic-clonic sz over 2 days
0007/0013-0007	24	m	500 mg 9 d		One sz. quetiapine continued. EEG normal.
0012/0029/2902*	55	f	4 d	flunitrazepam, diazepam, lormetazepam	
0012/0042/4203*	34	f	2 d	temazepam	Past history of seizure; completed 6 weeks without any more seizures
0015/0024/2408	38	f	75 mg 2 d	phenlypropanolamine	Syncope, hit head, later had seizure
0014/0059/5903*	50	m	500 mg 8 d		Grand mal convulsion; history of previous sz attributed to hypoglycemia, but serum glucose normal at time of this sz
0033OLE/0002/0001*	34	m	800 mg 5 mo		Past history of seizure; two seizures while on quetiapine (one following clonazepam withdrawal)
0007/0025/0009	27	f	550 mg 7 d		Past history of sz with chlorpromazine

0035/0001/0106	29	m	400 mg IR formulation 7 d	recent clozapine	Phase i study

* In primary integrated database

Patient 0013OLE/0006/0613, who had a seizure while hyponatremic, is described under metabolic adverse events. In addition, patient 0048/0007/0702, a 76 year old female, had unexplained syncope which was felt to have possibly been a seizure based on an EEG finding of sharp waves after the event and a Holter monitor evaluation negative for arrhythmia.

From the above table, it will be seen that 12/2387 (0.5%) of quetiapine exposed patients in the phase II-III primary integrated database experienced at least onc seizure. This incidence is comparable to the incidence in the control groups (see table in section 8.1.4).

Hostility

A search of the phase II-III primary integrated database (electronic data set 4msudbol/adversev) for the Costart term hostility as an adverse event deemed serious revealed only five such cases among quetiapine treated patients. (0014/0014/1444; 0014/0064/6410; 0048/0004/0405; 0048/0007/0709; 0048/0011/1102). No such events were reported among the control group patients. These data do not suggest that quetiapine treatment has a significant propensity to induce hostile behavior.

Suicidality and Depression

Please refer to the sponsor's data presented in section 8.1.4 above. Based on the sponsor's search of the ISS database (prior to the safety update), the rate of suicidality was actually lower with quetiapine than with the active control treatments or placebo. Of course, there is a potential source of bias if patients receiving open label quetiapine tended to be more stable than the acutely ill patients in the controlled trials. Similarly, the event rate for non-suicidal depression, listed in the sponsor's table as depression, was lower for the quetiapine treated patients, although the same bias is possible here as well.

Quetiapine treated patients 0012/0023/2303 and 0012 OLE/0067/6702 committed suicide, as well as one patient whose treatment remains blinded (please refer to appendix table 8.1.1.1).

8.2.6.3 Adverse nervous system events considered unlikely to be related to quetiapiene

The following lists such events. I have excluded serious adverse events that appeared to me to represent manifestations of a patient's underlying psychotic illness, such as agitation and the like. Not listed here, but shown in appendix table 8.1.1.1, are the quetiapine patients who died from cerebrovascular disease: 0012/0091/9103, and 0012OLE/0080/8013. Of course, if quetiapine is thrombophilic, as discussed previously under Cardiovascular System, deaths from stroke could be drug related.

Trial/subject	Event and comments
0048, Subject US-0013/1302	66 year old male collapsed due to weakness but did not have syncope; continued quetiapine
0012 OLE, Subject UK-0005/0502	38 year old female with schizophrenia hospitalized for manic reaction; was receiving paroxetine
0014 OLE Subject 0014/1402	32 year old male suffered concussion in an assault. Later hospitalized for anxiety
0012 OLE SubjectUK-0005/0506	41 year old female diagnosed as paranoid schizophrenic was hospitalized for mania, but resumed quetiapine without further manic symptoms
/0048, Subject US-0007/0713	80 year old man with Alzheimer's dementia hospitalized for aggression and agitation.
0048, Subject US-0007/0714	74 year old female with Alzheimer's dementia, while hospitalized for dehydration had a staring spell; neurological evaluation was negative but the patient was treated empirically with carbamazepine.
0012 OLE, Subject UK-0032/3203	31 year old male with paranoid schizophrenia hospitalized for mania
0013, Subject 0022/2204	65 year old male developed aphasia and dysarthria which resolved and were attributed to vertebrobasilar insufficiency. Blind not broken.
0012, Subject UK-0052/5204	28 year old female with schizophrenia hospitalized for insomnia
0014, Subject UK-0053/5312	46 year old female with chronic schizophrenia hospitalized for anxiety
0012 OLE, Subject 0087/8703	43 year old female with sciatica
0048, Subject US-0010/1015	66 year old female with bipolar disorder and multiinfarct dementia developed confusion, sedation, tachycardia, hypertension; also receiving lithium and clonazepam
0014 OLE/0064/6401	30 year old male with schizophrenia hospitalized after exposing himself in public
0012, Subject UK-0001/0104	44 year old male with malignant brain tumor (ependymoma) which became symptomatic on day 4 of quetiapine
0014 OLE, Subject 0069/6903	40 year old male diagnosed with brain tumor (probable ependymoma of 3rd ventricle) after 11 days of quetiapine
0015, Subject US-0003/0311	34 year old male hospitalized for alcohol and cocaine abuse
0048/0003/0307	75 year old man suffered a transient ischemic attack and was hospitalized for evaluation
0012/0029/2901	50 year old male with subdural hematoma

8.2.7 Respiratory

8.2.7.1 Adequacy of assessment of respiratory system events

To my knowledge, there were no chest X-rays or other special assessments of the respiratory system performed. Respiratory system adverse events were reported in the usual manner duriing clinical trials. In my opinon, this was adequate.

8.2.7.2 Respiratory System Adverse events Considered Possibly, probably, or Definitely Related to Quetiapine

There were no respiratory adverse events among the common and drug related events in the short term controlled trials.

Pneumonia

There were 3 deaths from pneumonia associated with quetiapine treatment: patients 0048/0007/0703 and 0048/0007/0708, as shown in appendix table, and an additional patient who died with pneumonia more than 30 days after quetiapine treatment had ended, patient 0048/0017/1703; in the last case the pneumonia began while the patient was receiving quetiapine.

The following table describes nonfatal cases of pneumonia during quetiapine clinical trials.

Table Summary of nonfatal pneumonias deemed serious adverse events associated with quetiapine (one patient not un-blinded)

Trial;subject	age	sex	quetiapine dose (mg) and duration	concomitant drugs	comments
5077IL/0031, US-0022/2204	52	m	BLINDED	glipizide,metformin, chloral hydrate, lorazepam	Left Lower Lobe Pneumonia
5077IL/0015OLE, US-0026/2614	65	m	600 mg 4 mo	lorazepam docusate, theopphylline	Left lower lobe pneumonia, sepsis, pneumoperitoneum of unkown etiology
5077IL/0048, US-0001/0114	87	m	600 mg 9 wk	betaxolol, carbidopa/ldopa,bromocriptine , chloral hydrate, lorazepam	Right lower lobe pneumonia Pt with dementia
5077IL/0048, US-0003/0308	80	f	450 mg 6 mo	ranitidine, Kcl, nifedipine, furosemide, ntg	pnuemonia
5077IL/0012OLE, UK-0042/4201	41	m	450 mg 8 mo		Bronchopulmonary infection required hospitalization
5077IL/0061 US-0001/0103	33	m			viral pneumonia, and pyelonephritis; discontinued
5077IL/0013OLE, CN-0022/2214	50	m	700 mg 79 d	Lovastatin, glyburide, lorazepam, sulindac, insulin	pnuemonia
204636/0008, UK-0019/0001	60	m	250 mg 7 d		bronchopneumonia

In addition, a submission to the Seroquel IND 7/11/96 noted 3 additional cases of pneumonia in quetiapine treated patients from after the NDA cutoff date (patient 0302 in study 0031, and patients 0308 and 0817 in study 0048).

Because pneumonia in the elderly is of particular concern, and because it has been proposed that neuroleptic treatment can be associated with aspiration pneumonia, the rate of pneumonia in quetiapine treated patients aged 65 years and older was calculated for the primary integrated

database. A total of 7 cases with the costart term pneumonia among patients of this age were identified in the primary integrated database(electronic search using CANDA data set 4msudbol:adversev). In addition, patient 0048/0007/0703 was found at autopsy to have had pneumonia even though pneumonia was not noted as an adverse event by the investigator. With a total of 190 quetiapine patients in this age range contributing 84.5 patient years of exposure, these 8 cases yield an incidence for pneumonia of 4.2 per 100 patients or 9.5 per 100 patient years for patients 65 years and older.

It has been suggested that neuroleptic use can increase the risk of pneumonia, perhaps through impairing swallowing with a consequently greater risk of aspiration (Bazemore PH, Tonkonogy J, Ananth R, *Dysphagia* 6:2-5, 1991). This may be the case for quetiapine.

8.2.7.3 Adverse respiratory events considered unlikely to be related to quetiapiene

Patient	Comments
0048 /0007/0712	64 year old man died with respiratory failure, aspiration in setting of progressive supranuclear palsy (after NDA cutoff date)
0048/0002/0201	70 year old male suffered exacerbation of chronic obstructive pulmonary disease.

8.2.8 Dermatological

8.2.8.1 Adequacy of assessment of dermatologic events

There were no particular diagnostic tests employed other than general physical examination to address dermatologic events. However, in my opinion this was adequate.

8.2.8.2 Adverse dermatologic events considered related to quetiapine

Rash was not a common, drug related adverse event in the quetiapine placebo controlled trials. Neither was the incidence of rash and allergic events increased over the control groups when expressed in terms of patient years, according to the sponsor's analysis (see table under section 8.1.4 above). Nonetheless, certain individual cases of rash that led to discontinuation of treatment were consistent with a drug etiology, as shown below.

Table Summary of rashes leading to discontinuation of quetiapine

Trial;subject	age	sex	quetiapine dose (mg) and duration	concomitant drugs	comments
0006, Subject US-0007/0703	32	f	75 mg x 2 d	lorazepam, oral contraceptive, chloral hydrate	Papular rash all extremeties, resolved after 4 days off quetiapine with antihistamine tx.
204636/0008, Subject US-0014/1406	59	m	13 d	chloral hydrate, lorazepam, acetaminophen	Nonpuritic, maculopapular rash on trunk and all extremities; concomitant lower extremity edema. Skin biopsy: perivascular lymphocytic infiltrate, possible leukoclastic vasculitis. Resolved after drug stopped.
5077IL/0015, Subject US-0024/2407	31	m	150 mg x 40 days	Albuterol, acetaminophen	Pruritic blotchy rash on trunk and extremities with leukocytosis and eosinophilia; rash deemed an allergic response by dermatologist. Treated with antihistamine and topical steroid.
5077IL/0013 OLE, Subject 0013/1304	21	m	500 mg x 7 days	vitamins, acetaminophen	Non pruritic, erythematous macular rash on trunk and extremities, resolved several days after drug stopped.
5077IL/0014 OLE, Subject 0003/0341	31	m	300 mg x 43 days	trifluoperazine	facial rash, no further details

Thus, while there was not a statistically apparent association of rash with quetiapine treatment in short term placebo controlled trials, certain of the clinical characterisitics of the individual cases noted above suggest a relationship to drug.

8.2.8.3 Adverse dermatologic events considered not likely to be related to quetiapine

Trial and subject	Event
5077IL/0012 OLE, Subject 0001/0119	Withdrawn for rash that proved to be scabies (Sarcoptes scabiei)
5077IL/0015, Subject US-0034/3411	hospitalized for treatment of cellulitis
5077IL/0048, Subject US-0008/0807	hospitalized for treatment of cellulitis

8.2.9 Special Senses

8.2.9.1 Adequacy of assessment of special senses

Mindful of the finding of cataracts associated with quetiapine treatment in dogs, the sponsor incorporated ophthalmologic assessments in the quetiapine clinical development program. This Division made recommendations about these assessments in a letter to the sponsor dated 1/5/90, and ophthalmologic surveillance was also discussed at the End of Phase II meeting with Zeneca. Slit lamp examinations were performed by ophthalmologists or optometrists during the course of many of the trials, with results catagorized simply as normal or abnormal. At Canadian sites, a more elaborate rating system was employed, the Lens Opacities Classification Scale

(LOCS III). This requires rating on four scales: cortical cataract, posterior subcapsular cataract, nuclear opalescence, and nuclear color. A normal exam is rated as 0.1, and top (i.e., worst) scores for each scale are up to 6.9. A grand total of 391 quetiapine subjects in controlled clinical studies had at least a baseline and followup slit lamp exam. For haloperidol and placebo treated patients, the numbers were 33 and 122, respectively. Certain open label trials also included slit lamp exams. During the one year controlled study 0015, examinations were obtained roughly every 3 months; given the gradual nature of the development of cataract, the long term study under protocol 0015 was considered the most relevant for evaluation of lens opacities.

The Division obtained consultation on this issue from Dr. Wiley Chambers of the Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550). In his opinion, the sponsor's monitoring for cataracts was inadequate. Please refer to his consult report for details.

8.2.9.2 Adverse special senses events Considered Possibly, probably, or Definitely Related to Quetiapine

Cataracts

Cataracts were associated with quetiapine exposure.of 3 months or longer in dogs. The findings included lens opacity after 3 months and development of posterior subcapsular cataracts at 6 months. Zeneca believes this to be the result of inhibition of cholesterol biosynthesis by quetiapine, leading to reduced cholesterol and increased cholesterol precursor sterols in the lens (and the blood). Monkeys did not show this toxicity.

In the pool of all controlled trials, the following numbers of patients had normal pretreatment slit lamp exams and abnormal on-treatment exams:

Quetiapine	11/391 (2.8%)
Haloperidol	1/33 (3.0%)
Placebo	3/122 (2.5%)

Ten of the eleven quetiapine patients with changes were enrolled in study 0015, the one year relapse prevention study.

For the LOCS III score results from placebo controlled trials, there was no clear cut pattern of lens abnormality associated with quetiapine treatment. One limitation of these data is that the majority of scores were obtained in the short term studies, so that late appearing effects would not necessarily be apparent.

With the CANDA data review function, all patients in the Phase II-III primary integrated database with a Costart term of "cataract specified" were identified (from data set 4msudbol: adversev). There were a total of 14/2387 (0.6%) quetiapine treated patients with this adverse event, none out of 206 placebo patients and 1/320 (0.3%) haloperidol treated patients. Expressed in terms of incidence per patient year of exposure, the incidence for quetiapine was 1.6 per 100 patient years, while the incidence for haloperidol was 2.4 per 100 patient years. The mean duration of treatment with quetiapine for these 14 patients was 276 days, and the mean age was 35 years, relatively young for age-related cataracts. For comparison, the overall mean duration of treatment with quetiapine in the phase II-III integreated primary database was 136 days (calculated from dataset 4msudbol:ddemog), and the mean age in the primary integrated database was 40 years. Thus patients with longer exposures were relatively overrepresented

among the patients identified as having cataracts; this could be consistent with a delayed drug effect or it could simply reflect a greater number of eye examinations performed during long term treatment.

Zeneca performed a somewhat broader search of the database for adverse events involving cataract, as shown in the following table.

TABLE Incidence of adverse events of cataract (adapted from sponsor's electronic ISS)**

Quetiapine (n = 2162) SY = 585.1		Quetiapine with safety update (n = 2387) SY = 865.3		Haloperidol (n = 320) SY = 42.3		Chlorpromazine (n = 100) SY = 9.2		Placebo (n = 206) SY = 14.6	
k (%)*	ER	k (%)*	ER	k (%)*	ER	k (%)*	ER	k (%)*	ER
15 (0.7)	2.6	16 (0.7)	1.8	1 (0.3)	2.4	0	0	0	0

*Number of subjects with adverse event (%).
SY = Subject years of follow up
ER = Event rate per 100 subject-years exposure
**cataract= cataract , cataract specified, eye disorder for investigators' terms that indicate cataract

The sponsor's search included more events than just those categorized under "cataract specified." The results were not markedly different from the results of the search I performed with the CANDA, however. Note that although the event rate for haloperidol exceeds that for quetiapine, this is because a single haloperidol patient developed cataract (patient 0015/035/03502, who had diabetes, underwent cataract surgery.) Diabetes is, of course, a risk factor for cataract.

With the help of Dr. Greg Burkhart, the relative risk and confidence limits were calculated for the adverse event of cataracts in study 0015, the one year controlled trial. The relative risk for the adverse event of cataract with quetiapine 600 mg/d compared to haloperidol was 1.4 (95% confidence limits 0.12-74 by Fisher exact), and for quetiapine 600 mg compared to the quetiapine 75 mg and 300 mg groups combined was 4.4 (95% confidence limit 0.35-228). Thus, the point estimate is consistent with an increased risk of cataracts, but the confidence limits are large and include the possibility of a reduced risk.

Dr. Chambers, in his consult report, notes that the small number of patients in the control groups makes comparisons of little value. Instead, he considered the proportion of patients receiving quetiapine who exhibited worsening on the LOCS III scale compared to patients whose scores improved; for both controlled trials and uncontrolled trials more patients worsened than improved. Reasoning that equal numbers would have worsened and improved by chance alone, Dr. Chambers concluded that these data are consistent with a drug effect.

Dr. Chambers has recommended that labeling for quetiapine carry a statement under Warnings regarding cataract development, and requiring periodic slit lamp exams for patients treated with quetiapine. Please refer to his consultation report for details.

8.2.9.3 Adverse special senses events considered unlikely to be related to quetiapine

There were no serious adverse events among quetiapine treated patients involving the special senses.

8.2.10 Genitourinary

8.2.10.1 Adequacy of assessment of genitourinary events

Clinical laboratories obtained during the quetiapine development program included urinalyses and assessment of BUN, creatinine and electrolytes. Spontaneously reported adverse events involving the genitourinary (GU) system were recorded as such. I am not aware of any special studies performed regarding the effects of quetiapine on renal function. In my opinion, the assessment of the GU system was less than adequate in one respect: for the two quetiapine treated patients who developed acute renal failure, the clinical information provided was very limited.

8.2.10.2 Adverse genitourinary events considered Possibly, probably, or Definitely related to quetiapine

There were no common and drug related adverse GU events in the short term placebo controlled trials; neither was any GU adverse event among the more common reasons for premature discontiuation. Findings from the pool of short term placebo controlled trials did not suggest any changes in serum BUN or creatinine, or urinalysis parameters associated with quetiapine treatment.

Nonetheless, two cases of acute renal fairlure were reportedwith quetiapine, in one case accompanied by profound anemia raising the possibility of renal failure secondary to hemolysis. While there is no specific evidence causally linking these cases to quetiapine, the meager clinical data provided do not establish a non-drug related cause for the renal failure, and so I have included them here.

Renal Failure

0048/0002/0201

70 year old man with congestive heart failure, hospitalized with acute renal failure attributed to concomitant trimethoprim-sulfa by sponsor. Patient simultaneously had profound anemia (hct 20), with total bilirubin of 8.6 umol/l at the time.

0012/0019/1903

33 year old white male, acute renal failure with hyponatremia and increased serum creatinine; renal function improved several days after d/c of quetiapine with after oral rehydration. Renal ultrasound was normal.

8.2.10.3 Adverse genitourinary events considered not likely to be related to quetiapine

Urinary retention

0012 OLE 0093/9308	20 year old female hospitalized for urinary retention; resolved 12 days after the d/c
0017 OLE US-0004/0401	85 year old male required foley catheter for urinary retention; resolved after drug d/c
0007, UK 0031/0003	42 year old female withdrawn for urinary retention

Other

0048 US-0008/0804	Elderly female developed urosepsis
0061 US-0001/0103	33 year old male developed viral pneumonia and pyelonephritis

8.2.11 Miscellaneous

8.2.11.1 Adequacy of assessment of miscellaneous adverse events

Not applicable.

8.2.11.2 Miscellaneous adverse events Considered Possibly, probably, or Definitely Related to Quetiapine

There were none.

8.2.11.3 Miscellaneous adverse events considered unlikely to be related to quetiapine

Deaths

Please refer to Appendix tables 8.1.1.1 and 8.1.1.1a.

A 40 year old male patient in a Japanese study was found dead; the investigator suspected water intoxication as a cause of death. The patient was receiving haloperidol.

The following deaths involved malignancy:
Patient 0015OLE/0005/0514 died from metastatic carcinoma with an unknown primary.
A 65 year old female in study 0048 who died from esophageal cancer and sepsis (after the NDA cutoff date).
A 69 year old male died from pancreatic carcinoma in study 0015 (after the NDA cutoff date).

Other:
Patient 0021/2104 in study 0031, whose treatment remains blinded, died from accidental drowining.
Patient 0012/0062/6203 escaped from the hospital and died in a car accident.

Nonfatal events:
Infections

5077IL/0012, Subject UK-0034/3404	34 year old female hospitalized for otitis
5077IL/0015 OLE, Subject 0005/0509	40 year old female with sepsis secondary to peridodontal abscess (not neutropenic)
5077IL/0012 OLE, Subject 0034/3404	34-year-old woman hospitalized due to a flare up of chronic otitis
5077IL/0014, Subject UK-0044/4402	25-year-old man with hospitalization due to severe ethmoidal sinusitis

Other

5077IL/0048, Subject US-0004/0404	75 year old man with syncope; negative work up; possible hypoglycemia (patient was on insulin)
5077IL/0048, Subject US-0016/1606	85 year old male underwent hernia repair
5077IL/0048, Subject US-0018/1813	78 year old female hospitalized for dehydration
5077IL/0015, Subject US-0005/0502	63 year old female with breast cancer

5077IL/0012 OLE, Subject 0080/8001	**24 year old female had surgery for benign cervical tumor**
5077IL/0015, Subject US-0027/2706	**30 year old male inhaled bleach fumes accidentally**
5077IL/0014 OLE, Subject 0014/1402	**32-year-old man with concussion and fractured nasal bone following assault**
5077IL/0014 OLE, Subject 0046/4601	**25 year old male hospitalized for EtOH intolerance and aggression**
5077IL/0013 OLE, Subject 0005/0508	**40 year old male ingested cleaning fluid (to "get younger")**
5077IL/0031, US-0009/0903-(blinded)	**42 year old male hospitalized with chest pain; MI was ruled out; possible GI etiology**

8.3 Summary of Key Adverse Findings

The following is a summary of important adverse events that are considered drug related. Please see the Review of Systems for more detailed data on each of the following adverse drug reactions.

Cardiovascular Adverse events

Postural hypotension and syncope: Postural hypotension was a common and drug related adverse event. Syncope, which is often a related phenomenon, occurred in roughly 1% of quetiapine treated patients.

Tachycardia: There were statistical increases in mean heart rate observed with quetiapine treatment in comparison to placebo, not limited to orthostatic-type changes in pulse.

QT interval prolongation: This was not consistently associated with quetiapine across clinical trials.

Thromboembolic events: There were a number of individual cases of deep vein thrombosis and stroke, raising the possibility that quetiapine treatment may be thrombophilic in certain patients.

Gastrointestinal

Increased liver enzymes: Asymptomatic increased liver enzymes were a common and drug related adverse event. No cases were documented to be symptomatic, although a nmber of patients were discontinued from quetiapine treatment for elevations in liver enzymes. What is not known, of course, is whether such discontinuations prevented more clinically significant cases of hepatic injury.

Dyspepsia and abdominal pain: These events were found to have a dose dependency in study 0013,and dyspepsia met the definition for common and drug related.

Hemic and lymphatic

Leukopenia/neutropenia: In a few patients, the clinical profile suggested a relationship between quetiapine treatment and decreased neutrophils or leukocytes. Four patients had ANC's less than 500; three recovered while on quetiapine and one was lost to followup but was later seen to be alive and well.

Anemia: Two patients had serious adverse events involving anemia, one with concurrent renal failure raising the possibility of hemolysis. Additional patients had severe anemia that was not considered a serious event. The clinical data provided regarding these cases are insufficient to draw inferences about the causal role of quetiapine treatment (additional information has been requested from Zeneca).

Metabolic and Endocrine

Hypothyroidism: Quetiapine treatment is associated with a decrease in thyroxine, but the clinical significance of this is not clear.

Weight gain: In short term placebo controlled trials, 23% of quetiapine treated patients had a weight increase of 7% or more.

Cholesterol and triglyceride elevation: Expressed as percent change from baseline, placebo controlled short term trial data show a mean increase of 11% for cholesterol and 17% for triglycerides with quetiapine treatment, without similar increases in the placebo group.

Hyperprolactinemia: There was little evidence for an association of quetiapine treatment with prolactin increase.

Neuroleptic malignant syndrome: There were 2 cases of possible NMS with quetiapine treatment.

Musculoskeletal system

Falls and fractures: These events may be tied to postural hypotension. Among patients over age 64, there was an incidence of 2.1%, or 4.7 per 100 patient years, for hip fracture associated with quetiapine treatment.

Nervous

EPS: quetiapine appears to induce generally modest EPS.

TD: quetiapine treatment has been associated with TD in some patients.

Somnolence: Somnolence was a common and drug related adverse event, with an incidence of 17.5% for quetiapine compared to 10.7% for placebo (p=0.0005). Somnolence did not show a statistically significant dose response relationship in either the long term fixed dose study (0015) or the short term fixed dose study (0013). Somnolence was the most frequently reported adverse event leading to premature discontinuation.

Convulsion: My review showed that 12/2387 (0.5%) of quetiapine exposed patients in the phase II-III primary integrated database experienced at least one seizure. The sponsor's incidence was somewhat higher (see table in section 8.1.4).

Respiratory

Pneumonia: There were 3 deaths from pneumonia among quetiapine treated patients. Among elderly patients receiving quetiapine, there was an incidence for pneumonia of 4.2 per 100 patients or 9.5 per 100 patient years for patients 65 years and older. Impairment of the gag reflex is a possible mechanism.

Rash: A number of individual cases of rash associated with quetiapine treatment had clinical or histological features suggesting a drug etiology.

Special senses

Cataracts: In preclinical studies there was a clear association between cataracts and quetiapine exposure. In clinical studies, 14 quetiapine patients had "cataract specified" recorded as an adverse event, with a mean age of 35 years among these 14 patients. The relative infrequency of lens abnormalities makes comparisons between treatment groups of limited inferential value. Dr. Chambers from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products has recommended that patients on quetiapine therapy have periodic slit lamp examinations.

Genitourinary

Acute renal failure: This was reported in 2 quetiapine treated patients; available clinical information is insufficient to draw inferences about the role of quetiapine treatment in these cases.

9.0 Labeling Review

I will comment briefly on a few labeling issues.

Clinical Pharmacology: The inclusion of a lengthy discussion of PET study results is questionable, in my view. I am inclined to agree with the statement about lack of prolactin elevation, however.

Clinical Trials: The sponsor has overstated the results at a few points with respect to comparisons that did not achieve statistical significance, but this is generally a balanced presentation.

Warnings: I do not believe that the labeling should suggest a reduced potential for tardive dyskinesia.

Regarding NMS, using the adjective "rare" may be too reassuring and it might be better to state the actual number of possible NMS cases (n=2).

Labeling regarding cataracts and thyroid abnormalities is needed. With respect to cataracts, I believe the labeling should recommend slit lamp examinations as indicated by Dr. Chamber's consult review, unless the sponsor can make a more persuasive case to forgo such monitoring.

The overdosage section of labeling requires revision. There have now been 7 reports of quetiapine overdosage. The precautions about QT prolongation described in the labeling, which appear to have been adapted from the Risperdal labeling, may be unnecessary for this compound.

11.0 Conclusions

The sponsor has provided evidence from adequate and well controlled studies establishing the efficacy of quetiapine in the treatment of acutely ill schizophrenic patients. There are no safety issues that cannot be addressed with appropriate labeling or that would adversely affect the risk-benefit assessment for quetiapine.

12. Recommendations

This NDA is approvable, in my opinion.

At this time, a request for additional clinical information about patients with certain adverse events is pending. If the sponsor has not responded by the time of the approvable letter, a request should be made in the letter.

The sponsor should be asked to perform an adequate relapse prevention study.

6/13/97

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