AstraZeneca

Amended Clinical Study Protocol	
Drug Substance	quetiapine fumarate
Study Code	5077IL/0089
Edition No.	3
Date	[redacted]

A multicenter, open-label, flexible-dose, parallel-group evaluation of the cataractogenic potential of quetiapine fumarate (SEROQUEL™) and risperidone (RISPERDAL™) in the long-term treatment of patients with schizophrenia or schizoaffective disorder

AstraZeneca Clinical Development Team representative

[redacted]

AstraZeneca Research and Development site representative

AstraZeneca Research and Development site representative

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	[redacted]		
2	[redacted]		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1	[redacted]		

ASTRAZENECA EMERGENCY CONTACT PROCEDURE

In the case of a medical emergency you may contact the Clinical Study Team Leader. If the Clinical Study Team Leader is not available, contact the Clinical Study Physician at the AstraZeneca Research and Development site show below.

Role in the study	Name	Address and telephone number
Study Delivery Leader	[redacted]	[redacted]
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CRO Contact Information

Role in the study	Name	Address and telephone number
Project Manager	[redacted]	[redacted]

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Clinical Lead	[redacted]	[redacted]
Medical Advisor	[redacted]	[redacted]
Project Manager [redacted])	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

For further clarifications regarding:

- Procedures in case of medical emergency see Section 9.2.
- Procedures in case of overdose see Section 9.3.
- Procedures in case of pregnancy see Section 9.5.

Protocol synopsis

A multicenter, open-label, flexible-dose, parallel-group evaluation of the cataractogenic potential of quetiapine fumarate (SEROQUEL™) and risperidone (RISPERDAL™) in the long-term treatment of patients with schizophrenia or schizoaffective disorder

Investigator

TBD

Study center(s) and number of patients planned

The total number of patients expected to be randomized to study drugs and procedures are approximately **1000**. There will be approximately 90 centers. Approximately 1600 patients will be screened to achieve the goal of 1000 randomized patients

Study period		**Phase of development**
Estimated date of first Patient enrolled	[redacted]	Phase IV
Estimated date of last Patient completed	[redacted]	

Objectives

Primary:

To evaluate the relative cataractogenic potential of quetiapine and risperidone with respect to nuclear opalescence (N), cortical (C) or posterior subcapsular opacification (P) for events over 2 years of exposure.

Secondary:

To characterize the long-term safety and tolerability of quetiapine and risperidone as measured by adverse events, clinical laboratory assessments, physical exams, electrocardiograms (ECGs), Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS).

To characterize the long-term treatment effects on efficacy using the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions (CGI) and relapse criteria for quetiapine in comparison with risperidone.

To compare time to first relapse of schizophrenia or schizoaffective disorder.

To characterize the long-term treatment effects on quality of life using the Quality of Life Enjoyment and Satisfaction Short Form (QLESSF) and Personal Evaluation of Transitions in Treatment (PETiT) for quetiapine in comparison with risperidone.

Hypothesis

Primary Hypothesis:

The 2-year event rate for cataractogenic events, nuclear opalescence (N), cortical (C) or posterior subcapsular opacification (P) measured by the LOCS II criteria for quetiapine treated patients is non-inferior to the rate in risperidone treated patients, where patients take 2 years of study drug (at least 21 months exposure).

Secondary Hypotheses:

Quetiapine has comparable efficacy compared to risperidone.

Quetiapine has superior safety, tolerability and patient satisfaction compared to risperidone.

Study design

This study is a 24-month, multicenter, evaluator masked (ophthalmologist), open-label, flexible-dose, parallel-group study to compare the cataractogenic potential of quetiapine and risperidone in patients with schizophrenia or schizoaffective disorder. In an intent to treat approach, patients discontinuing study treatment will continue to have eye examinations to detect any cataractogenic changes every 6 months for a 2-year period (24 months).

Target patient population

Male and female patients between the ages of 18 and 65 with the DSM-IV diagnostic criteria of schizophrenia or schizoaffective disorder.

Investigational product, dosage and mode of administration

Patients randomized to quetiapine fumarate (SEROQUEL™) will be titrated as follows: 50 mg on Day 1, 100 mg on Day 2, 200 mg on Day 3, 300 mg on Day 4, 400 mg on Days 5 through 7, 600 mg on Day 8; thereafter the dosage will be adjusted for efficacy and tolerability to within the dosing range of 200 to 800 mg/day. Study drug will be administered orally twice-daily using **25 mg** and **100 mg tablets** during titration, and following titration (Day 8 onwards) quetiapine **100 mg tablets** may be given BID or TID (for TID the drug can be given in an uneven divided doses) as instructed by the investigator.

Comparator, dosage and mode of administration

Patients randomized to risperidone (RISPERDAL™) will be administered 2 mg/day on Days 1 through 5, 3 mg on Days 6 and 7, and 4 mg on Day 8; thereafter the dosage will be adjusted for efficacy and tolerability to within the dosing range of 2 to 8 mg/day. Study drug will be

administered orally twice-daily using 1 **mg tablets** during titration, and following titration (Day 8 onwards) risperidone may be given BID or QD as instructed by the investigator.

Duration of treatment

Patients will participate for 2 years (104 weeks).

Outcome variables

Primary

Presence/absence of cataractogenic events in patients with 2 years of exposure (minimum 21 months) including patients withdrawn for an event. Events of N, C or P as agreed by 2 independent treatment masked non-consulting ophthalmologists at the 24-month visit or earlier for patients who withdrew due to the event.

Secondary

1. Incidence, severity and causality of Extrapyramidal Symptoms (EPS), adverse events, other adverse events (OAEs), serious adverse events (SAEs) and withdrawals due to adverse events.

2. Changes in vital signs, clinical laboratory assessments, physical examination, and ECGs from baseline to each assessment visit.

3. Investigator rating scales for extrapyramidal effects: SAS, BARS and AIMS from baseline to final assessment.

4. PANSS total score, at each assessment and change from baseline.

5. PANSS positive subscale score, at each assessment and change from baseline.

6. PANSS negative subscale score, at each assessment and change from baseline.

7. PANSS psychopathology subscale score, at each assessment and change from baseline.

8. CGI Severity of Illness score, at each assessment and change from baseline.

9. CGI Global Improvement, at each post baseline assessment.

10. Change in total score for QLESSF from baseline and each assessment.

11. Change in total score of PETiT from baseline and each assessment.

12. Time to first relapse of schizophrenia or schizoaffective disorder.

13. Number of relapses of schizophrenia or schizoaffective disorder.

Statistical methods

In order to assess the cataractogenic potential, the upper 95% confidence limit will be calculated for the between-treatment differences assuming a binomial distribution. Unconditional exact test for the confidence interval on difference of proportions will be used (Santner & Snell 1980; Berger & Boos 1994).

Per-protocol analyses for the cataractogenic potential will be used to assess these non-inferiority comparisons.

Kaplan-Meyers survival analysis methods will be used to descriptively compare the time to cataractogenic event for both treatments.

Descriptive statistics will be used for safety endpoints; analysis of covariance will be used for analysis of continuous variables such as labs, vital signs, ECGs, SAS, BARS, and AIMS.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1 Abbreviations and specialist terms

Abbreviation or specialist term	Explanation
AE	Adverse Event (see definition in Section 4.6.3.1).
AIMS	Abnormal Involuntary Movement Scale
AZ	AstraZeneca Pharmaceuticals LP
BARS	Barnes Akathisia Rating Scale
BID	Twice Daily
C	Cortical Opacification standard for LOCS II
CBC	Complete Blood Count
CGI	Clinical Global Impression
CRF	Case Report Form
CSA	Clinical Study Agreement
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ECGs	Electrocardiograms
EPS	Extrapyramidal Symptoms
Eye Examination	Slit Lamp Evaluation with LOCS II including pupil dilation measurement and Best Visual Acuity
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H_1	Histamine receptor site
HCG	Human Chorionic Gonadotropin
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IPS	Investigational Products Section
IRB	Institutional Review Board
IVRS	Interactive Voice Response System

Abbreviation or specialist term	Explanation
kg	Kilograms
LOCS II	Lens Opacities Classification System II
m^2	Meter squared
mg	Milligrams
ml	Milliliters
mm	Millimeters
N	Nuclear opalescence standard for LOCS II
OAE	Other significant adverse event (i.e., an adverse event of special interest in this clinical development; see definition in Section 4.6.4.1). AstraZeneca Clinical Study Physician will perform the classification of OAEs after the study is complete.
OU	Both eyes
P	Posterior subcapsular opacification standard for LOCS II
PP	Per Protocol Population
PANSS	Positive and Negative Syndrome Scale
PETiT	Personal Evaluation of Transitions in Treatment
PI	The Principal investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
QD	Once Daily
QDS	Quantitative Decision Science
QLESSF	Quality of Life Enjoyment and Satisfaction Short Form
SAE	Serious Adverse Event (see definition in Section 4.6.4.1).
SAS	Simpson-Angus Scale
TID	Three times a day
TSH	Thyroid-Stimulating Hormone
UA	Urinalysis
UDS	Urine Drug Screen
USI	Universal Systems Incorporated
USP	United States Pharmacopeia
WBC	White Blood Cells

1. INTRODUCTION

1.1 Background

This Phase IV, randomized, parallel-group study is designed to evaluate the cataractogenic potential of quetiapine fumarate (SEROQUEL™) compared with that of a putative non cataractogenic antipsychotic medication risperidone (RISPERDAL™). This study is being conducted to fulfill the SEROQUEL Phase IV commitment regarding evaluation of cataractogenic potential.

1.2 Preclinical

In dogs given quetiapine fumarate for 6 and 12 months, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg/day, or 4 times the maximum recommended human dose on a mg/m^2 basis. In a 1-year study in Cynomolgus monkeys, a striated appearance of the anterior lens surface was detected in 2 of 7 females at a dose of 225 mg/kg/day, or 5.5 times the maximum recommended human dose on an mg/m^2 basis. No cataracts were observed in monkeys dosed up to 225 mg/kg/day or in rodents.

No drug-related opacities were seen in rats or mice after 2 years of exposure to quetiapine fumarate. Exposure to quetiapine fumarate, as the parent compound, was higher in dogs than in the rodents. In the 1-year study in monkeys, the exposure to quetiapine fumarate and some principal metabolites at a quetiapine dose of 225 mg/kg/day was similar to that found at a dose of 100 mg/kg/day in the 1-year dog study.

1.3 Clinical

During the pre marketing clinical development program, no consistent pattern of lens changes was observed in patients during long-term treatment with quetiapine. A causal relationship between any lens changes and quetiapine use could not be established; however, the possibility of lenticular changes could not be excluded at the time the new drug application for quetiapine was approved. As a result, examination of the lens by methods adequate to detect cataract formation, such as slit lamp examination or other appropriately sensitive methods, is recommended at treatment initiation or shortly thereafter and at 6 month intervals during chronic treatment.

Since its approval in September 1997 through July 31, 2005, it was estimated that about 13.8 million patients worldwide (an estimate of almost 9.4 million patients in the US and 4.4 million patients ex-US) have been exposed to SEROQUEL through 31 July 2005 for US and through fourth quarter 2004 for ex-US. Independent ophthalmologic review of approximately 200 case reports of cataracts received by AstraZeneca from the clinical development phase through December 31, 2004 revealed no evidence of direct linkage to quetiapine treatment. This conclusion is based on the absence of an apparent relationship to dose or duration of quetiapine therapy, the lack of demonstration of uniformity in lens pathology (location and

type of pathology), and absence of indication of consistent bilateral lens pathology (data on file).

1.4 Rationale for this study

Data obtained from patients in this clinical study using the LOCS II grading (Chylack et al 1989) will evaluate the cataractogenic signal suggested by the preclinical data. The study is being conducted to fulfill the SEROQUEL Phase IV commitment regarding evaluation of cataractogenic potential.

2. STUDY OBJECTIVES

2.1 Primary objective

To evaluate the relative cataractogenic potential of quetiapine and risperidone with respect to nuclear opalescence (N), cortical (C) or posterior subcapsular opacification (P) for events over 2 years of exposure.

2.2 Secondary objectives

To characterize the long-term safety and tolerability of quetiapine and risperidone as measured by adverse events, clinical laboratory assessments, physical exams, electrocardiograms (ECGs), Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS).

To characterize the long-term treatment effects on efficacy using the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions (CGI) and relapse criteria for quetiapine in comparison with risperidone.

To compare time to first relapse of schizophrenia or schizoaffective disorder.

To characterize the long-term treatment effects on quality of life using the Quality of Life Enjoyment and Satisfaction Short Form (QLESSF) and Personal Evaluation of Transitions in Treatment (PETiT) for quetiapine in comparison with risperidone.

3. HYPOTHESES, STUDY PLAN AND PROCEDURES

3.1 Hypotheses

Primary:

The 2-year event rate for cataractogenic events, nuclear opalescence (N), cortical (C) or posterior subcapsular opacification (P) measured by the LOCS II criteria for quetiapine treated patients is non-inferior to the rate in risperidone treated patients, where patients take 2 years of study drug (at least 21 months exposure).

Secondary:

Quetiapine has comparable efficacy compared to risperidone.

Quetiapine has superior safety, tolerability and patient satisfaction compared to risperidone.

3.2 Overall study design and flow chart

This study is a 24-month, multicenter, evaluator masked (ophthalmologist), open-label, flexible-dose, parallel-group study to compare the cataractogenic potential in patients treated with quetiapine versus risperidone, in patients with schizophrenia or schizoaffective disorder. This study will be conducted on an outpatient basis. In an intent to treat approach, patients discontinuing study drug will continue to have eye examinations including slit lamp assessments to detect any cataractogenic changes every 6 months for a 2-year period (24 months from enrollment into the study).

More than 1000 men and women with a diagnosis of schizophrenia or schizoaffective disorder will be enrolled into the study (approximately 535 in the quetiapine group, and approximately 465 in the risperidone group will reach the 6-month eye examination), with the assumption that at least 170 patients in each treatment group (340 total) will remain in the study for 2-year and be evaluable. The number of patients was calculated in the following fashion: Assuming 40% of patients will complete at least 21 months of treatment without significant protocol violations or deviations, the assumptions of 535 quetiapine patients and 465 risperidone patients will be necessary to obtain 170 evaluable patients per treatment group. To account for an expected 5% drop out rate before the 6-month eye examinations including slit lamp assessments and 10% rate of unevaluable patients due to protocol violations and deviations, approximately 535 quetiapine patients and 465 risperidone patients will be enrolled.

Patients will be randomly assigned to receive either quetiapine or risperidone. Randomization will be stratified, based on 2 age categories (<40 years, 40 years or older) and on 3 categories of prior or current exposure to study treatment (current or prior exposure to quetiapine, current or prior exposure to risperidone, current or prior exposure to both drugs or neither drug).

If a patient enters the study on quetiapine or risperidone and is subsequently randomized to the same drug, he or she may continue on the dose prescribed as long as it is within the guidelines below.

- If the prior dose of quetiapine is less than 600mg/day or if the prior dose of risperidone is 4mg/day, then patient must be titrated upward

- Risperidone may be taken BID or QD depending upon the investigator's discretion.

Patients randomized to quetiapine will be titrated from Days 1 – 8 (as specified in Section 3.5.1.2); thereafter the dosage will be adjusted for efficacy and tolerability to within the dosing range of 200 to 800 mg/day. Study drug will be administered orally twice-daily using **25 mg** and **100 mg tablets** during titration, and following titration (Day 8 onwards) quetiapine **100 mg tablets** may be given BID or TID (for TID the drug can be given in an uneven divided

doses) as instructed by the investigator. Doses may be modified to improve tolerability or to enhance therapeutic efficacy.

Patients randomized to risperidone will be titrated from Days 1 – 8 (as specified in Section 3.5.1.2); thereafter the dosage will be adjusted for efficacy and tolerability to within the dosing range of 2 to 8 mg/day. Study drug will be administered orally twice-daily using 1 **mg tablets** during titration, and following titration (Day 8 onwards) risperidone **1 mg tablets** may be given BID or QD as instructed by the investigator. Doses may be modified to improve tolerability or to enhance therapeutic efficacy.

All patients must be cross-tapered off of all of their previous antipsychotic medication. The exact schedule of this will be at the investigators discretion.

The schedule of screening and study procedures is shown in Table 2 (Study Plan). Patients will be randomized to study treatment only after all screening procedures for eligibility have been conducted and the patient is deemed appropriate to participate in the study. The visit schedule must be adhered to as closely as is clinically possible, a window of ± 3 days for visits 3-5 at the clinic, a window of ±7 Days for monthly visits and +30 days for an eye examination is allowed. If the timing of a visit does not conform to the study schedule for visit intervals, subsequent visits should follow the protocol schedule relative to the start of treatment.

Retaining patients on study drug for a 2 year period and obtaining the scheduled lens examinations will be critical to the study's success. Each investigative site will participate in the development and implementation of a site-specific patient retention strategy, agreed upon by the sponsor and the Quintiles site monitor.

Figure 1 Study flow chart

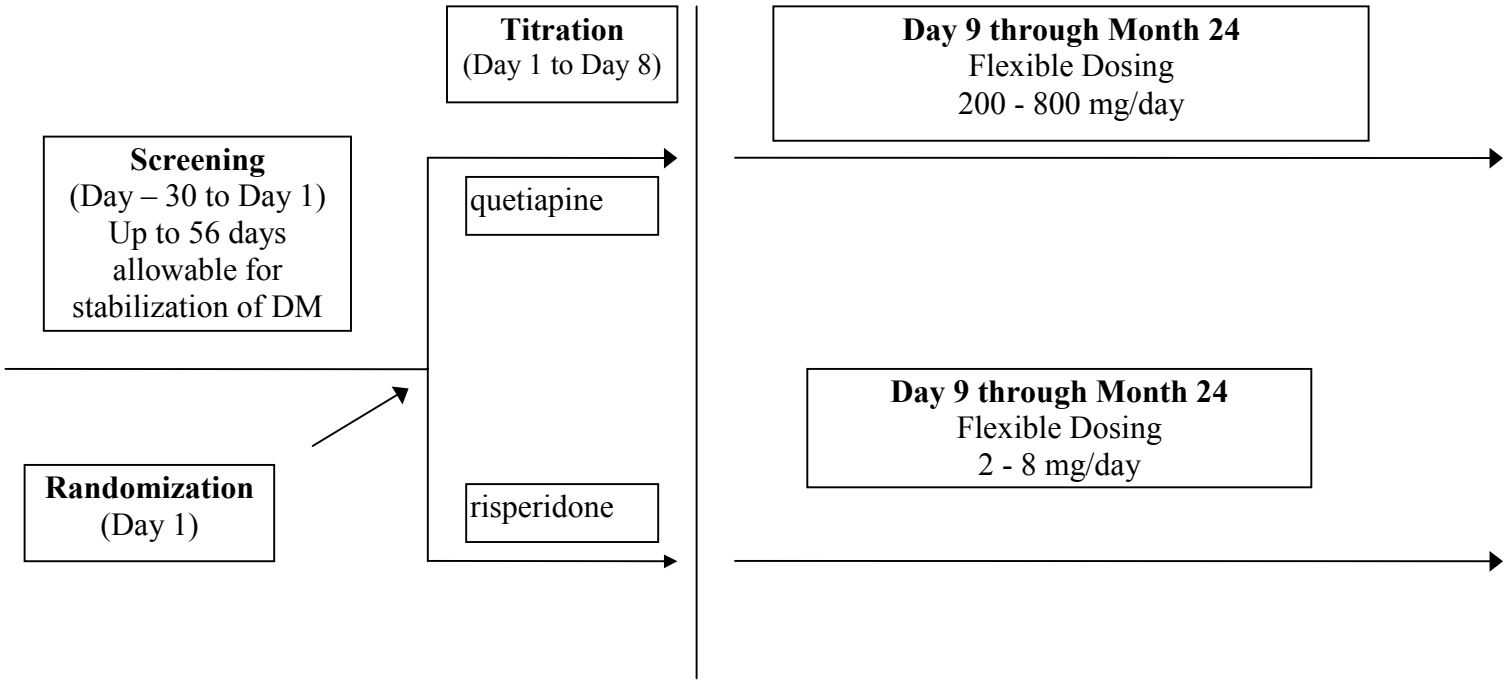

Table 2 Study plan

Event	Screening [a]	Day 1	Day 7	Day 14	Day 30	Weekly (every 7 days)	Monthly (every 30 days)	Quarterly (every 3 months)	Every 6 months	At Completion or consent withdrawal	Continuation after study drug withdrawn (every 6 months)
Visit [b]	**1**	**2**	**3**	**4**	**5**		**6-28**	**7, 10, 13,16, 19, 22, 25**	**10, 16, 22**	**Final (visit 28)**	
Informed consent, demography, medical, psychiatric history, diabetes risk factor and cataract risk factors	√										
Eye examinations[c]	√								√	√	√
Psychiatric evaluation	√										
Physical examination	√									√	
Vital signs/Weight[k]	√	√	√	√	√		√			√	
Prior Medication	√	√									
Blood collection for clinical chemistry[af], thyroid function tests, lipid profile[af], and prolactin level[l]	√							√		√	
Hemoglobin A1c	√							√		√	
Serum Insulin[af]	√							√		√	
Hematology (CBC with differential & Absolute Neutrophils Count)[j]	√				√		√	√		√	
Genotyping [d] Urine Drug Screen	√										
Urinalysis	√									√	
Clinical Global Impression Severity of Illness and Global Improvement[g]		√			√		√			√	
Serum Pregnancy Test [l]	√							√		√	
Dispensing of Study Drug		√	√	√	√		√				
Randomization		√									
Positive and Negative Syndrome Scale (PANSS)		√						√		√	

Event	Screening [a]	Day 1	Day 7	Day 14	Day 30	Weekly (every 7 days)	Monthly (every 30 days)	Quarterly (every 3 months)	Every 6 months	At Completion or consent withdrawal	Continuation after study drug withdrawn (every 6 months)
Visit [b]	**1**	**2**	**3**	**4**	**5**		**6-28**	**7, 10, 13,16, 19, 22, 25**	**10, 16, 22**	**Final (visit 28)**	
12-lead electrocardiogram	√								√	√	
Modified Simpson-Angus Scale (SAS)		√						√		√	
Barnes Akathisia Rating Scale (BARS)		√						√		√	
Abnormal Involuntary Movement Scale (AIMS)		√						√		√	
Quality of Life Questionnaire (QLESSF)		√						√		√	
Personal Evaluation of Transitions in Treatment (PETiT)		√						√		√	
Telephone call from sites						√					
Adverse Events[h]	√	√	√	√	√		√			√	√
Concurrent medications	√		√	√	√		√			√	√
Drug compliance			√	√	√		√			√	

[a]All screening evaluations will be done within 30 days prior to randomization. If a patient has DM the screening period may be extended to a maximum of 56 days in order to stabilize the Patients diabetes medication. If laboratories were collected > 30 days before randomization, they must be repeated before the patient is randomized.
[b]Window of ±3 days for visits 3-5 and ± 7 days visits 6-28.
[c]Eye examinations, including slit lamp assessments with LOCS II and best visual acuity, must be completed within +30 days of visit. patients may discontinue the drug treatment portion of the study and continue to participate in the eye examination portion of the protocol. Eye examinations will be performed any time a Patient discontinues.
[d]Genotyping is optional and the patient must sign a genetic informed consent.
[e]A UDS may be done after visit 1 at the investigators discretion. Patients with a positive urine drug screen (UDS) will have a repeat UDS within 7 - 21 days. If the repeat UDS is positive, with the exception of cannabinoids, the patient will be excluded.
[f]Blood samples for clinical chemistry should be obtained under fasting conditions. Fasting is defined as not having ingested food or liquid other than water for > 8hrs. Fasting blood sample should be obtained before noon.
[g]Global Improvement not done at the baseline visit (visit 2).
[h]AEs and SAEs will be collected throughout the study, even for those patients that will discontinue study drug but continue in the ophthalmologic portion of the study.
[i]Investigators may repeat at any visit if clinically indicated.
[j]If the patient presents with a fever, pharyngitis, or other signs and symptoms of infection at any time, a CBC with differential should be completed.
[k]Blood pressure, pulse, respiration rate, temperature, height and weight will be obtained at Visit 1 and completion or consent withdrawal. Blood pressure, pulse rate, temperature and weight will be obtained at all other visits. Blood pressure and pulse will always be obtained in both the supine and standing positions.
[l]Prolactin level is obtained at screening and completion or consent withdrawal.

3.3 Rationale for study design, doses and control groups

The study is designed to evaluate the cataractogenic potential of quetiapine employing a non-inferiority method against a comparator (risperidone), which is putatively non-cataractogenic.

Such a design is adequate to demonstrate long-term safety and is consistent with the recent report and recommendations of the National Bioethics Advisory Commission (1998).

The risperidone dose will be titrated to 2-8 mg per day to be dosed flexibly based on efficacy and tolerability. Quetiapine will be titrated to 200-800 mg per day. This represents dosing according to both compounds prescribing information (Physicians Desk Reference 2005 59th edition).

3.4 Selection of study population

3.4.1 Study selection record

The investigators must keep a record of patients who were screened for enrollment but who were never randomized to study drug, i.e. a patient screening/enrollment log.

3.4.2 Inclusion criteria

For inclusion in the study patients must fulfill all of the following criteria:

1. Provision of written informed consent.

2. Men and women age 18 to 65 years.

3. Documented clinical diagnosis meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for any of the following:

Schizophrenia type	DSM-IV code
Catatonic	295.20
Disorganized	295.10
Paranoid	295.30
Undifferentiated	295.90
Residual	295.60
Schizoaffective disorder	295.70

4. Clinically stable enough to be treated in an outpatient setting, in the opinion of the investigator.

5. Ability, in the investigator's opinion, to cooperate with repeated eye examinations.

6. Removed.

7. Stable place of residency prior to Visit 1 in the opinion of the investigator.

8. Negative pregnancy test. Fertile female patients must use a reliable method of birth control, i.e. barrier method, oral contraceptive, implant, long-term injectable contraceptive, intrauterine device, tubal ligation or abstinence.

9. Both eyes present with lenses intact (no previous cataract extractions).

10. Qualifying LOCS II slit lamp score assessment by 2 independent treatment-masked ophthalmologists.

3.4.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. History, or evidence of narrow angle glaucoma

2. Evidence of significant eye disease, which may require treatment in the study treatment period, as judged by the ophthalmologist.

3. Legal blindness (defined as best corrected visual acuity of 20/200 or worse in one or both eyes) prior to randomization.

4. Previous removal of a cataract in 1 or both eyes (or absence of a lens).

5. History of corneal surgery.

6. Evidence of significant eye infection.

7. Baseline/screening lens asymmetry of 0 and 2, or 1 and 2 for nuclear opalescence by either eye grader.

8. Baseline/screening lens rating greater than 0 for posterior subcapsular opacification, greater than 1 for cortical opacification or greater than 2 for nuclear opalescence by either eye grader.

9. Baseline/screening lens rating disagreement of 0 and 2, or 1 and 2 by the 2 eye graders regarding nuclear opalescence.

10. Patients for whom dilation of pupil to a minimum of 6 mm is not feasible.

11. History of significant traumatic injury to either eye.

12. Treatment for eye injury or eye disease within the past 30 days prior to randomization.

13. Continuous treatment with systemic steroids (oral, intravenous or inhaled) for greater than 3 months over the patient's lifetime.

14. Any medical illness likely to require chronic or frequent treatment with corticosteroids.

15. Treatment within the past 3 months with phenothiazines.

16. Current treatment with psoralens.

17. Current treatment with allopurinol.

18. Medical or psychiatric illness that would interfere with ability to comply with protocol.

19. More than three hospitalizations for psychiatric illnesses in the past 12 months.

20. History of non-compliance suggesting inability to comply with protocol.

21. Diagnosis of any secondary DSM-IV Axis I disorder, unless that secondary disorder, in the investigator's judgment, is stable and not the primary focus of treatment.

22. Administration of a depot antipsychotic injection within 1 dosing interval (for the depot) before Day 1.

23. Positive urine drug screen for illicit substances (excluding cannabinoids), or drug or alcohol dependence.

24. Clinically significant deviations from the reference range in screening clinical laboratory test results as evaluated by the investigator.

25. Evidence of significant medical conditions, such as advanced cancer, HIV infection, liver, renal or heart disease, which may require hospitalization or other major interventions during the course of the study or which may later affect the pharmacokinetics of the study drugs administered.

26. History of known non-responsiveness to quetiapine or risperidone.

27. Participation in another drug study within 4 weeks prior to Day 1 of this study.

28. Previous participation in this study.

29. Known intolerance to quetiapine or risperidone.

30. Use of potent cytochrome P450 3A4 inhibitors or inducers at least 14 days prior to randomization (See Appendix E)

31. Clinically significant ECG as evaluated by the investigator.

32. An absolute neutrophils count (ANC) of $<1.5 \times 10^9$/L.

33. A patient with unstable or inadequately treated Diabetes Mellitus (DM), defined as:

- HgA1c >8.5% at enrollment
- Admitted to hospital for treatment of DM or DM related illness within in the past 12 weeks preceding enrollment
- Not under the care of a physician responsible for the patient's diabetes management.
- Not having the approval of the physician responsible for the patient's diabetes management.
- Not being on the same dose of oral hypoglycemic drug(s) and/or diet for the 4 weeks prior to randomization. For thiazolidinediones (glitazones) this period should not be less than 8 weeks.
- Taking insulin whose daily dose on one occasion in the past 4 weeks has been more than 10% above or below their mean dose in the preceding 4 weeks.

Note: If a diabetic patient meets one of these criteria the patient is to be excluded even if the treating physician believes that the patient is stable and can participate in the study.

3.4.4 Restrictions

There are no restrictions other than the inclusion and exclusion criteria listed above and concurrent medications listed in Section 3.5.3.

3.4.5 Discontinuation of patients from treatment or assessment

3.4.5.1 Criteria for Discontinuation

Patients may be discontinued from study treatment and subsequent psychological assessments at any time. Following study treatment withdrawal, patients will be followed for eye examinations every 6 months for the protocol specified 2 years unless a cataractogenic event has occurred or the patient has withdrawn consent. Specific reasons for discontinuing a patient from study drug are:

1. Voluntary discontinuation by the patient who are at any time free to discontinue their participation in the study.
2. Non-compliance to the protocol as judged by the investigator and/or AstraZeneca.
3. Development of exclusion criteria, e.g., pregnancy.
4. The occurrence of an adverse event, which, in the opinion of the investigator, warrants patient withdrawal.

5. The patient is lost to follow-up (unable to reach the patient after 3 documented phone calls and one certified letter sent).

6. The patient experiences a cataractogenic event.

7. Lack of efficacy of the patients' schizophrenia or schizoaffective disorder as judged by the investigator.

8. Development of study-specific discontinuation criteria.

9. A confirmed ANC of $< 1.5 \times 10^9$ / L, which is confirmed by repeat testing.

Discontinuation of Study Drug Only

1. If a patient has an absolute neutrophil count $< 1.5 \times 10^9$ / L, repeat the test within 24 hours.
   If it remains $< 1.5 \times 10^9$ / L, discontinue the drug.

3.4.5.2 Procedures for discontinuation

The reason for discontinuation and the date of discontinuation from the study must be documented on the CRF provided. The effect of discontinuation will be considered in the analysis to minimize potential bias. For all discontinuations, the full assessments that are specified at the end of the study period should be carried out whenever possible. All adverse events must be reported, but in particular any adverse event leading to discontinuation from the study. All discontinuations due to a serious adverse event must be reported to **AstraZeneca** or the **CRO within 24 hours (1-day)**.

Patients may withdraw consent for genetic research whether or not they choose to continue participation in the clinical trial. If a patient withdraws consent for genetic research, his or her genetic sample will be destroyed, but if research on the sample has already been performed, the resulting genetic data will not be destroyed. (In fact, all remaining genetic samples will be destroyed 15 years following completion of the clinical trial; see Section 4.7 for further details).

The following assessments must be completed at study discontinuation: eye examination including slit lamp evaluation with LOCS II and best visual acuity), physical examination, fasting blood collection, hemoglobin A1c, hematology, urinalysis, serum pregnancy test, serum glucose, serum insulin, 12-lead ECG, CGI including Global Improvement, PANSS, SAS, BARS, AIMS, QLESSF, PETiT, adverse events, concurrent medications, and drug compliance.

3.5 Treatments

3.5.1 Investigational products

AstraZeneca will provide centers with open-labeled supplies of both commercial comparator drug (risperidone) and quetiapine. The study drug will be supplied as tablets for oral use as follows: See Table 3.

3.5.1.1 Identity of investigational product and comparators

Table 3 Study drug

Treatment	Formulation number	Presentation
quetiapine 25 mg	F12804	Peach round tablet
quetiapine 100 mg	F12689	Yellow round tablet
risperidone 1 mg	F12860	White oval tablet

3.5.1.2 Doses and treatment regimens

If a patient enters the study on quetiapine or risperidone and is subsequently randomized to the same drug, he or she may continue on the dose prescribed as long as it is within the guidelines below. All medications, during the initial dose titration (day 1-8) must be taken BID. If the prior dose of quetiapine is less than 600mg/day or the prior risperidone dose is less than 4mg/day the patient must be titrated upward.

Quetiapine

Quetiapine will be taken orally and should generally be administered with an initial dose of 50 mg on Day 1, 100 mg on Day 2, 200 mg on Day 3, 300 mg on Day 4, 400 mg on Days 5 through 7, 600 mg on Day 8; thereafter the dosage will be adjusted for efficacy and tolerability to within the dosing range of 200 to 800 mg/day. Further dosage adjustments, up to 800 mg should generally occur at intervals of not less than 2 days, as the steady state for quetiapine would not be achieved for approximately 1-2 days in the typical patient. Study drug will be administered orally twice-daily using **25 mg** and **100 mg tablets** during titration, and following titration (Day 8 onwards) **100 mg tablets** may be given BID or TID (for TID the drug can be given in an uneven divided doses) as instructed by the investigator.

Consideration should be given to a slower rate of dose titration and a lower target dose in patients who have a predisposition to hypotensive reactions. When indicated, dose escalation should be performed with caution in these patients. For additional information regarding quetiapine, please refer to the package insert in Appendix F.

Risperidone

Risperidone will be administered 2 mg/day on Days 1 through 5; 3 mg on Days 6 and 7; and 4 mg on Day 8; thereafter the dosage will be adjusted for efficacy and tolerability to within the dosing range of 2 to 8 mg/day. During titration phase study drug will be administered orally

using 1 mg tablets BID and following titration (Day 8 onwards) 1mg of risperidone may be given BID or QD as instructed by the investigator.

Consideration should be given to a slower rate of dose titration and a lower target dose in patients who have a predisposition to hypotensive reactions. When indicated, dose escalation should be performed with caution in these patients. For additional information regarding risperidone, please refer to the package insert in Appendix G.

Table 4 Dosing schedule for study drug

Drug	**Quetiapine***			**Risperidone***		
Time	AM	PM	Total Dose	AM	PM	Total Dose
Day 1	1 x 25 mg	1 x 25 mg	50 mg	1 x 1 mg	1 x 1 mg	2 mg
Day 2	2 x 25 mg	2 x 25 mg	100 mg	1 x 1 mg	1 x 1 mg	2 mg
Day 3	1 x 100 mg	1 x 100 mg	200 mg	1 x 1 mg	1 x 1 mg	2 mg
Day 4	1 x 100 mg	2 x 100 mg	300 mg	1 x 1 mg	1 x 1 mg	2 mg
Day 5	2 x 100 mg	2 x 100 mg	400 mg	1 x 1 mg	1 x 1 mg	2 mg
Day 6	2 x 100 mg	2 x 100 mg	400 mg	1 x 1 mg	2 x 1 mg	3 mg
Day 7	2 x 100 mg	2 x 100 mg	400 mg	1 x 1 mg	2 x 1 mg	3 mg
Day 8	3 x 100 mg	3 x 100 mg	600 mg	2 x 1 mg	2 x 1 mg	4 mg

3.5.1.3 Labeling

Quetiapine and risperidone will be packaged into bottles. The risperidone 1 mg tablets will be removed from the commercial bottle and repackaged into a High Density Polyethylene (HDPE) bottle with induction seal closure. The bottles and closures for quetiapine and risperidone will be identical. All products for this trial will be provided in bulk bottles with tablet quantities dependent on the stage of the trial. The bottles will be labeled with a two-panel open-label that contains at least the following information: study number, product name, number of tablets/bottle, and storage condition. Upon distributing bottle(s) to each patient, the right portion of the two-panel label will be removed from the bottle(s) and affixed to the patient's permanent record. All supplies will be packaged and labeled by AstraZeneca. The treatment bottles will be clearly marked as "Clinical Study Material".

Patients will have treatment randomly allocated through an IVRS system based on the central stratified randomization schedule. The randomization number will be entered onto the Eligibility Case Report Form. Patient number, patient initials, date drug dispensed, visit

number and center number will also be added to the Case Report Form (CRF) at the time of dispensing. It is the responsibility of the investigator to ensure that accurate accountability records are maintained throughout the study.

3.5.1.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions.

All study drugs will be stored in their original containers at controlled room temperature (20 to 25 degrees Celsius; 68 to 77 degrees Fahrenheit; see USP) and protected from moisture. Risperidone must also be protected from light.

3.5.1.5 Accountability

It is the investigator/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products so as to ensure that:

- Deliveries of such products from AstraZeneca are correctly received by a responsible person (e.g. a pharmacist).
- Such deliveries are recorded.
- Study treatments are handled and stored safely and properly.
- Study treatments are only dispensed to study patients in accordance with the protocol.
- Any unused products are returned to USI for destruction.

At the end of the study it must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist.

It is essential that all study drugs be accounted for by the investigator or institution, and that any discrepancies are explained and documented.

The study treatment(s) must be used only as directed in the protocol and are to be prescribed by only the investigator or the sub-investigator(s) named on the FDA 1572 Form. The investigator must maintain accurate records accounting for the receipt of the investigational products and for the disposition of the material. This record keeping consists of a dispensing record including the identification of the person to whom the drug is dispensed, the quantity, the date of dispensing, and any unused drug returned to the investigator. This record is in addition to any drug accountability recorded on the CRFs.

Patients must return all unused study drug and empty containers to the investigator. The number of tablets returned must be checked against the number dispensed to determine patient compliance.

The investigator will retain the returned study drug until AstraZeneca or the CRO authorized personnel collect it, along with any study treatments not dispensed. At the termination of the study or at the request of the sponsor, all unused drug supplies will be returned by AstraZeneca or the CRO to USI for destruction. This return will be documented by using a Study Drug Return Form supplied by AstraZeneca.

3.5.2 Method of assigning patients to treatment groups

This study will employ a central stratified randomization. The actual treatment given to individual patients will be determined via an IVRS system. The randomization schedule will be prepared by the QDS Group of AstraZeneca to be incorporated into the IVRS system. There will be a 2x3 way stratified randomization based on 2 age categories, age (<40 vs. >=40 years) and on 3 categories of current or previous exposure to risperidone, current or previous exposure to quetiapine, and current or previous exposure to both drugs or neither drug. In order to ensure at least 170 patients in each treatment group at the 2-year evaluation, the ratio of quetiapine to risperidone patients will be increased from 1:1 to 2:1 for the final months of recruitment (approximately the last 4 to 6 months). This would result in a slight imbalance at randomization with approximately 535 patients randomized to quetiapine and 465 patients randomized to risperidone, but should result in similar numbers reaching the 2 year assessment point.

Patients will be assigned a patient number at the time of consent; this number will be unique to the patient. Once a patient number has been assigned, no attempt should be made to use that number again if, for example, a patient withdraws or is withdrawn from the study. No patient should be enrolled twice into the study.

Each eligible patient will be assigned a randomization number based within a stratum based on the central randomization schedule. If a patient is dispensed the incorrect treatment, AstraZeneca or the CRO and the IVRS service should be notified of the error. No attempt should be made to remedy the error once study material has been dispensed. The patient will continue with the dispensed study material. AstraZeneca or the CRO should be notified as soon as the error is discovered. Subsequent patients will continue using the first unallocated number in the original numbering sequence for the stratum.

The eligibility of each patient will be established against the inclusion/exclusion criteria for the study before randomization. Patients will be randomized centrally and sequentially within the strata, as patients are eligible for randomization. If a patient discontinues the study drug, the patient number will not be reused, and the patient will be encouraged to remain in the study for ophthalmologic endpoints.

3.5.3 Pre-study, concurrent and post-study treatment(s)

Treatment with an antidepressant or mood stabilizer is allowed with the exception of those described in Appendix E. Concomitant antipsychotic medications and drugs such as psoralens and allopurinol known to cause cataracts are prohibited; these must be tapered off as described in Section 3.2. . See Appendix E for additional prohibited medications.

Other psychotropic medications, including antidepressants and mood stabilizers, which are considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator(s). Concomitant medication must not violate any exclusionary criteria. The administration of all medication (including study drug) must be recorded in the appropriate sections of the CRF.

During the course of the study, the following medications will also be permitted, if clinically necessary:

- If severe psychotic symptoms occur the dose of study drug should be increased up to the maximum allowable dose for this study. If symptoms remain severe, haloperidol may be given either orally or intramuscularly as needed for adjunctive treatment for a maximum cumulative total of 30 days. The haloperidol should be tapered off when symptoms have improved.

- Oral benztropine mesylate (up to 6 mg/day) may be administered for the treatment of extrapyramidal symptoms (EPS). Prophylactic use of benztropine mesylate is permitted at the investigators discretion.

3.5.4 Treatment compliance

Patients must return all unused study drug and empty containers to the study site. The number of tablets issued minus the number of tablets returned will be used to calculate the tablets taken.

Compliance = (tablets taken during the period ÷ prescribed number of tablets) x 100

Example: 800 mg prescribed dose for a 28-day period

8 (100 mg) tablets/day for 28 days = 224 tablets prescribed and the patient took 175 tablets

Compliance = (175/224) x 100 = 78%, which would require counseling for compliance

Any patient taking less than 80% of the prescribed study drug at 2 consecutive visits will be considered non-compliant. Patients will continue in the study but will be counseled on the importance of taking their study drug regularly. Compliance will be checked at each study visit. Fully compliant patients will rate $\geq$ 80%, partially compliant patients will rate $\geq$ 70% and non-compliant patients will rate < 70 %. To check for compliance and assist in patient retention, weekly contact (e.g. telephone calls to the patient) will be required.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Primary variable

4.1.1 Cataractogenicity

Primary assessment: LOCS II in vivo grading of the lens via slit lamp examination with documented protocol-specific minimum extent of pupillary dilation by 2 independent, treatment-masked ophthalmologists trained in the use of LOCS II. These assessments will be made at pre-treatment baseline and every 6 months thereafter for 24 months or when the patient discontinues study participation, if the patient has already had the six-month ophthalmological examination.

Primary measures: LOCS II grades of 0, 1, 2, 3, or 4 for nuclear opalescence (N), LOCS II grades of 0, tr (trace), 1, 2, 3, 4, or 5 for cortical opacification (C) and LOCS II grades 0, 1, 2, 3, or 4 for posterior subcapsular opacification (P).

Primary outcome variable: Presence/absence of cataractogenic events in patients with 2 years of exposure (minimum 21 months) including patients withdrawn for an event. Events of N, C or P as agreed by 2 independent treatment masked non-consulting ophthalmologists at the 24-month visit or earlier for patients who withdrew due to the event.

4.2 Screening and demographic measurements

The following data will be collected in the case report form:

- Date of birth, gender, and race.
- Significant medical, surgical and psychiatric history.
- Concurrent Medications
- Physical examination.
- Risk factors for the development of cataracts include: age, gender, race, smoking, diabetes mellitus, family history of cataracts, previous eye surgery, previous eye injury or inflammation (>30 days of screening), outdoor occupation with exposure to sunlight (>2 years), radiation therapy, and a family history of diabetes.
- Eye examination including slit lamp evaluation with LOCS II (see Section 4.6.2.1, Methods of Assessment)
- Family history of Diabetes
- Weight

- Vital Signs
- Best Visual Acuity
- Psychiatric evaluation
- Previous history of current or prior exposure of risperidone, quetiapine, and/or both, or neither.
- 12-lead ECG

4.3 Patient-Reported Outcomes (PROs)

The QLESSF, quality of life instrument and PETiT will be self-reported by the patient. These questionnaires will be completed at quarterly visits (every 3 months) to the investigational site.

Table 5 Patient Reported Outcomes relating to each objective

Objective	Variables	Significance of results
To characterize the long-term treatment effects on quality of life using the Quality of Life Enjoyment and Satisfaction Questionnaire (QLESSF) and Personal Evaluation of Transitions in Treatment (PETiT) for quetiapine in comparison with risperidone.	Descriptive statistics include QLESSF total and PETiT total. PETiT treatment acceptability sub-total.	Quetiapine demonstrates improved patient reported outcomes compared to risperidone.

4.4 Health Economic measurements and variables

4.4.1 QLESSF

4.4.1.1 Methods of assessment

The QLESSF is a 16-item questionnaire that will be completed by the patient at visits to the investigational site. Each item is rated by the patient according to a 5 point satisfaction level scale from 1=very poor to 5=very good. Higher scores reflect higher overall life enjoyment and satisfaction. The QLESSF will be assessed at baseline (visit 2 – day 1), quarterly (every 3 months) and at completion or consent withdrawal.

4.4.1.2 Derivation or calculation of variable

A total score will be calculated by summing the scores for the 16-items. Change from baseline will be derived at each assessment.

4.4.2 PETiT

4.4.2.1 Methods of assessment

The PETiT is a 30-item questionnaire that will be completed by the patient upon arrival at the investigational site, and prior to any structured interview. Each item is rated by the patient according to a 3 point frequency rating scale: 2=often, 1=sometimes, 0=never. The PETiT will be assessed at baseline (visit 2 – day 1), quarterly (every 3 months) and at completion or consent withdrawal.

4.4.2.2 Derivation or calculation of variable

The PETiT will be calculated for the 30-items using a standard algorithm to rescale items. The total score will be calculated and a 6-item subtotal for treatment acceptability. Changes from baseline will be calculated for each assessment time for both total and 6-item subtotal.

4.5 Efficacy and pharmacodynamic measurements and variables

Efficacy is a secondary objective of this study. Table 6 shows how the efficacy **variables** of this study relate to the study objectives.

Table 6 Efficacy objectives and variables relating to each objective

Objective	Variables	Significance of results
To characterize the long-term treatment effects on efficacy using the PANSS, the CGI and relapse criteria for quetiapine in comparison with risperidone.	**Secondary**: Descriptive statistics and graphical representation of: PANSS Total Score PANSS Positive Subscale Score PANSS Negative Subscale Score PANSS Psychopathology Subscale Score CGI Severity of Illness CGI Global Improvement Relapse Criteria Assessment Time to first relapse of schizophrenia or schizoaffective disorder	Quetiapine is comparable to risperidone in control of schizophrenia symptoms as measured by PANSS and CGI assessment scales. The time to event Kaplan-Meyers survival curves for time to relapse are similar for quetiapine and risperidone.

At each center, whenever possible the same rater will administer a specific psychiatric assessment at all study visits in order to reduce variability in rating-scale scoring. This individual conducting the PANSS will be certified to conduct the rating scale by participating in a training program approved by AstraZeneca.

4.5.1 PANSS Total Score

4.5.1.1 Method of assessment

The PANSS is a 30-item instrument that will be used to rate the patient's symptoms of psychosis. Scoring for each of the items will be on a 1- to 7-point scale with 1 indicating that an individual symptom was "absent" and 7 indicating that the symptom was manifested to an "extreme" degree.

4.5.1.2 Calculation or derivation of outcome variable

The PANSS Total score will be calculated by summing the scores from each of the 30-items. Changes from baseline in the PANSS Total score will be calculated by subtracting the baseline (Visit 2) total score from the visit score.

4.5.2 PANSS Positive Subscale Score

4.5.2.1 Methods of assessment

The PANSS Positive score is the total score of PANSS items: Delusions, Conceptual Disorganization, Hallucinatory Behavior, Excitement, Grandiosity, Suspiciousness/Persecution and Hostility.

4.5.2.2 Calculation or derivation of outcome variable

The PANSS Positive score will be calculated by summing the scores from each of the 7 items. Change from baseline in the PANSS Positive score will be calculated by subtracting the baseline (Visit 1) Positive score from the visit score. Alleviation of positive psychotic symptoms will be indicated by a negative change score.

4.5.3 PANSS Negative Subscale Score

4.5.3.1 Methods of assessment

The PANSS Negative score is the total of 7 PANSS items: Blunted Affect, Emotional Withdrawal, Poor Rapport, Passive/Apathetic Social Withdrawal, Difficulty in Abstract Thinking, Lack of Spontaneity and Flow of Conversation and Stereotyped Thinking.

4.5.3.2 Calculation or derivation of outcome variable

The PANSS Negative score will be calculated by summing the scores from each of the 7 items. Change from baseline in the PANSS Negative score will be calculated by subtracting the baseline (Visit 1) Negative score from the visit score. Alleviation of negative psychotic symptoms will be indicated by a negative change score.

4.5.4 PANSS General Psychopathology Subscale Score

4.5.4.1 Methods of assessment

The PANSS general psychopathology score is the total score of 16 PANSS items: Somatic Concern, Anxiety, Guilty Feeling, Tension, Mannerism and Posturing, Depression, Motor Retardation, Uncooperativeness, Unusual Though Content, Disorientation, Poor Attention,

Lack of Judgment and Insight, Disturbance of Volition, Poor Impulse Control, Preoccupation and Active Social Avoidance.

4.5.4.2 Calculation or derivation of outcome variable

The change from baseline in the PANSS General Psychopathology score will be calculated by subtracting the baseline (Visit 1) General Psychopathology score from the visit score. Alleviation of general psychopathology symptoms will be indicated by a negative change score.

4.5.5 CGI Severity of Illness

4.5.5.1 Methods of assessment

The CGI is a 3-part instrument; only the first 2 parts will be used in this study. The Severity of Illness scale is scored to rate the patient's current clinical state.

4.5.5.2 Calculation or derivation of outcome variable

The scores for the CGI Severity of Illness subtest ranges from 1 to 7 such that a score of 1 indicates "normal, not ill at all," while a score of 7 indicates "among the most extremely ill patients." The change from baseline of the Severity of Illness will be calculated by subtracting the baseline score from the visit score. Alleviation of symptom severity will be indicated by a negative change score.

4.5.6 CGI Global Improvement

4.5.6.1 Methods of assessment

The second part of the CGI, the Global Improvement scale, is scored to rate the patient's change from baseline. This assessment will be done at visit 5, monthly (every 30 days) and at completion or consent withdrawal.

4.5.6.2 Calculation or derivation of outcome variable

The scores for the CGI Global Improvement scale ranges from 1 to 7 such that a score of 1 indicates "very much improved," while a score of 7 indicates "very much worse." Symptomatic improvement from status at entry into the study will be indicated by scores of 3 or less while symptomatic deterioration will be indicated by scores of 5 or more. A CGI Global Improvement score of "very much improved" or "much improved" will be indicated by a score of 1 or 2.

4.5.7 Relapse

4.5.7.1 Methods of assessment

Interview of the patient at each visit as to any hospitalizations during the intervening period. A review of the CGI Severity assessment as compared to the patient's baseline evaluation.

4.5.7.2 Calculation or derivation of outcome variable

Relapse will be defined as a binomial response variable with values of 1 for presence and 0 for absence. The criteria to be used to define relapse are as follows: 1) a hospitalization for psychiatric symptoms associated with the patient's diagnosis or 2) an increase of 2 units on the CGI Severity rating at the visit compared to baseline.

The date of the first determination of relapse will be captured. Time to first relapse will be calculated as the difference between the date of first relapse and the date of first dose of study drug. Patients with no relapse at the time of final assessment will have their time to relapse censored at using the date of last observation.

4.6 Safety measurements and variables

4.6.1 Summary of safety objectives and variables

Table 7 shows how the safety **variables** of this study relate to the study objectives.

Table 7 Safety objectives and variables relating to each objective

Objective	Variables	Significance of results
The primary objective of this study is to evaluate the relative cataractogenic potential of quetiapine and risperidone with respect to nuclear opalescence (N), cortical (C) or posterior subcapsular opacification (P) for events over 2 years of exposure.	Primary: Events of N, C or P at the 24-month visit, including events reported at earlier slit lamp examination visits (conducted every 6 months) for patients who withdrew due to the event.	Quetiapine is non-inferior to risperidone, an atypical agent without cataractogenic potential, with respect to cataractogenic potential at 2 years.
Secondary: To characterize the long-term safety and tolerability of quetiapine and risperidone as measured by adverse events, clinical laboratory assessments, physical exams, ECGs, SAS, BARS, and AIMS.	Number and percent of adverse events (all, drug related, serious, leading to withdrawal) Vital signs Weight Laboratory assessments Physical examinations ECG assessments SAS BARS AIMS	Quetiapine is superior to risperidone in assessments of EPS symptoms reported as adverse events or assessment by SAS, BARS or AIMS. Both quetiapine and risperidone are safe during long-term use.

4.6.2 Cataractogenic Assessments

4.6.2.1 Methods of Assessments

The methods for collecting cataractogenic safety data are described below.

Eye examinations will be performed by one of the study ophthalmologists at the designated ophthalmology centers. This will include assessment of visual acuity and the anterior chamber. Approximately 45 such centers will participate in the study; at each center, 2 ophthalmologists will perform examinations on patients referred by psychiatric investigative sites located in the surrounding area. Following randomization, the ophthalmologists will be masked to treatment assignment. The ophthalmologists will not be made aware of each other's ratings of the patient.

Visual acuity

A visual acuity examination (best corrected vision) will be performed for each eye using the Snellen Eye Chart at baseline, every 6 months, and upon study termination. A trained technician may perform visual acuity exams. If best-corrected vision wearing eyeglasses is not 20/20, then refraction should be performed. Data captured should include sphere, cylinder and axis OU.

Pupil dilation

Prior to administration of any ophthalmic solution, the ophthalmologist will examine the anterior chamber to assess the potential of narrow angle closure glaucoma. The pupil will be dilated; the dilating agent and the number of drops administered will be at the ophthalmologist's clinical judgment. Patients will be encouraged to close their eyes after administration of the drops for about 3-5 minutes to reduce the stinging sensation. Anesthetic drops should be used to reduce the stinging sensation. Before proceeding with the lenticular examination, the examiner will verify that the pupil fully dilated to a minimum of 6.0 mm. If pupillary dilation is less than 6.0 mm, on the baseline/screening exam, the patient will be excluded from the study.

Slit-lamp examination

A transparency of the LOCS II standards will be placed on a light box mounted at shoulder level, and behind the Patient seated at the slit lamp. The room lights will be dimmed. Slit-lamp examination may be conducted in the usual manner using varying slit-beam intensities and angles to discover the location in the lens of all components of any existing cataract. However, when a cataract is graded, the examiner will be restricted to a 45° slit angle for the nuclear assessment and a 0° angle (which creates a uniformly illuminated retroillumination or red reflex view) for cortical and subcapsular assessment.

The slit height and width of the slit lamp (9mm x 3mm) at the 45°angle should be adjusted so that the overall brightness of the corneal image and anterior subcapsular zone approximate those of the nuclear color and opalescence standard (N). At the 0° angle the brightness should enable the examiner to see all of the opacities without discomfort for the patient.

When performing LOCS II classification, the grader will assess the presence or absence and the severity of opacification or opalescence in the cortex, nucleus and posterior subcapsular zones. For the assessment of the cortical and posterior subcapsular cataract, the aggregate extent of the opacity as seen by the retroillumination view will be used to calculate the total grade. The feature used to assess severity of nuclear cataract will be opalescence, the milky quality of the nucleus, seen in the slit lamp view. Three areas will be graded: nuclear opalescence (N), cortical (C) and posterior subcapsular opacification (P); details of each are described below.

Grading of the nuclear opalescence:

Nuclear opalescence will be graded by comparing the opalescent quality of the nuclear region itself to standard images N-0, N-I, N-II, N-III, and N-IV. The color should be disregarded when assessing nuclear opalescence. The slit-lamp width should be the same as that used when grading nuclear color. The N grade should always be the level equal to or less than the standard. A grade of N-I will be assessed if the average opalescence is more than the N-0 standard but less than or equal to the N-I standard. For the purpose of grading, the average density of the opacity across the entire nucleus will be the prime consideration rather than the size of the nuclear opacification.

Grading of cortical and posterior subcapsular opacities:

Cortical opacities will be graded using 7 cortical standards: C-0, C-tr (trace), C-I, C-II, C-III, C-IV, and C-V. For nuclear opalescence, grade will be defined as that grade which is equal to or less than the grade standard. Cortical opacity will be more complex to grade because there are multiple levels, and the appropriate grade is based on combined opacification. Therefore, if there are multiple small separate opacities, the observer must estimate the combined total area to properly grade for cortical opacity.

Posterior subcapsular opacities are often granular or vacuolar and located in the area just beneath the posterior capsule. They are usually discoid or irregularly discoid in shape. These opacities should not be confused with a Mittendorf dot if noted for the patient. Grades range from P-0, P-I, P-II, P-III, and P-IV and are defined as less than or equal to the standard. A grade of P-0 should be assigned if no opacity is present against the red reflex view. Sometimes with an obliquely angled slit beam, a (P) opacity may be visible, but if it is not visible with the retroillumination view, it should be graded as P-0.

The first ophthalmologic examiner should manually record their findings on the patient specific worksheet document. They are then to phone in the results of the LOCS II assessment, recording their findings using the ICON IVRS technology. Each site will be provided a user manual regarding the IVRS system. This will include identifiers for the site, the ophthalmologist, and the patient, and 6 scores corresponding to both eyes and the three cataract assessments (N, C, P).

In a similar fashion, after the 2nd ophthalmologic examiner completes their slit lamp exam, they manually record their findings, and then phone in the data to the same IVRS system. After entering the patient's LOCS II scores, the second examiner must wait for a response

from the automated system. If there is agreement on the patient scores by the 2 examiners (the IVRS system detects that there is a consensus about a cataractogenic event, or a non-event), the patient may leave. If there is not an agreement (the IVRS system detects that one examiner reported an event, but the other did not), the patient must be re-examined by both ophthalmologists and another manual recording completed, then the same IVRS procedure to document the results must be repeated separately by each ophthalmologists. This slit lamp re-examination and documentation of information should be done promptly, so the patient's eyes do not have to be re-dilated for the repeat assessment.

It is critical for the integrity of the blind that the ophthalmologic examiners do not discuss their findings with each other at any time, nor should they review previous assessments they have made of the patients lens status at earlier visits.

After the repeat slit lamp assessment by both ophthalmologists and the recording of the results in the IVRS by both examiners, the patient may leave. The ophthalmology center is to fax a confirmation of the completed slit lamp examination to the psychiatric site the patient was referred from. They are also to fax any AE/SAE reported to them to the psychiatric site for appropriate documentation and follow up. The IVRS sponsor (ICON) will fax documents to the ophthalmology center, confirming successful electronic transmission of the LOCS II data, and to the psychiatric site addressing the patient's eligibility to enter the study (for the baseline/screening exam). If the IVRS system detected there was an agreement on a cataractogenic event after the 1st exam, or when re-examined after an initial disagreement between ophthalmologists, an alert will be triggered to AstraZeneca and to the Quintiles Medical Monitor, who will contact the psychiatric site where the patient was referred from and inform them to discontinue the patient from the trial.

Lack of agreement between graders on a lens change that meets criteria at each visit will be monitored and will be addressed with additional LOCS II training, if warranted.

4.6.2.2 Calculation or derivation of outcome variables

Three primary safety measures will be evaluated in the assessment of cataractogenic potential. These measures are the proportions of evaluable patients with N, C or P events. An event will be defined using the LOCS II grading scale as applied by 2 independent, treatment-masked, ophthalmologists trained in the use of the LOCS II.

For each patient, a type-specific cataractogenic event is defined as a specified increase in lens opacification according to the LOCS II grading system as determined by both ophthalmologists (See Table 8). Specifically, an event of N is a lens change from a baseline/screening nuclear opalescence grade of 0 or 1 to N 2 or greater, or a lens change from a baseline/screening nuclear opalescence grade of 2 to grade N 3 or greater; an event of C is a lens change from a baseline/screening cortical opacification grade of 0, trace, or 1 to grade C 2 or greater; and an event of P is a lens change from a baseline/screening posterior subcapsular opacification grade of 0 to grade P 1 or greater.

At the baseline/screening slit lamp examination the 2 graders need not agree on the LOCS II grading for a patient to be included in the study and randomized, however, any baseline/screening lens rating greater than 2 for N, greater than 1 for C, or greater than 0 for P by even 1 grader will result in patient exclusion. However, there must be the following degree of concordance regarding nuclear opalescence: ratings by the two ophthalmologic graders must be 0 and 1, or 2 and 2 for the patient to be eligible for the trial. In the first instance, subsequent grades of 2 or higher would constitute a cataractogenic event; in the latter instance, subsequent grades of 3 or higher would constitute a cataractogenic event. Thus, if the baseline/screening slit lamp examination scores are 2 and 1, or 2 and 0 by the two ophthalmologists regarding nuclear opalescence, the patient is not eligible for the trial, as the criteria for an event would be different between the two ophthalmologists for subsequent exams.

If there is a disagreement about a lens change fulfilling event criteria at subsequent (every 6 months) eye examinations for N, C or P and a re-examination by the two ophthalmologist raters, still blinded to each other's scores, does not result in agreement, the patient may be continued in the study (See Table 9). If the patient withdraws from the study medication prematurely, and no termination/end of study or follow-up slit lamp assessments are available, the determination by a single grader of a lens change meeting event criteria at the patient's last slit lamp examination will be counted as an event. If follow-up slit lamp assessments are available, but no event is evident, then the longer drug exposure without an event overrides the earlier "event", irrespective of whether there was agreement between graders or not.

Time to event for the LOCS II defined cataractogenic event will be calculated as the date of event – date of study entry. For patients without an event the time will be censored at the patient's end of study visit.

Table 8 Definition of Cataractogenic Event

		Nuclear (N)		**Cortical (C)**	**Posterior (P)**
Baseline/Screening Assessment		Grade of 0 or 1 (not a cataractogenic event)* ↓	Grade of 2 (not a cataractogenic event)+ ↓	Grade of 0, tr, 1 (not a cataractogenic event) ↓	Grade of 0 (not a cataractogenic event) ↓
Additional Assessments	**Event**	Grade of 2 or greater	Grade of 3 or greater	Grade of 2 or greater	Grade of 1 or greater
	Non-event	Grade <2	Grade <3	Grade <2	Grade <1

*Both ophthalmologists must agree to grade of 0 or 1 at baseline; + both ophthalmologists must agree to grade of 2 at baseline.

Table 9 Process of Ophthalmologists assessment on LOCS II criteria for cataractogenic event

Study Visit	Agreement	Disagreement
Baseline/Screening Slit Lamp Assessment	Below baseline LOCS II criteria ↓ Yes ↓ randomize	Do not reassess, if one examiner determines LOCS II criteria have been met for N, C, P, but the other examiner does not ↓ exclude from study
	At or above LOCS II criteria ↓ Yes ↓ exclude from study	
Subsequent Slit Lamp Assessments (6, 12 & 18 month)	Below LOCS II criteria for event ↓ Yes ↓ continue with study	• Repeat slit lamp assessment. • If now agree, continue with study if below event criteria or terminate if at or above the event criteria • Disagree again, continue in trial
	At or above LOCS II criteria for event ↓ Yes ↓ terminate from study	
End of study (24 month) or Termination Slit Lamp Assessment	Below LOCS II criteria for event ↓ Yes ↓ no event	• Repeat slit lamp assessment • If now agree: event or non-event • Disagree again, if at end of study assessment (at least 21 months of study medication were taken) → terminate; presence/absence of event defined by analysis criteria
	At or above LOCS II criteria for event ↓ Yes ↓ event	

4.6.3 Adverse Events

4.6.3.1 Definitions

The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this. For the purpose of this study, cataractogenic events will be considered as adverse events, even though they are end points for the study.

Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. **Unsolicited AE reports occurring up to 30 days after last dose of investigational drug should be recorded together with concomitant medications in appropriate sections of the CRF. AEs will be collected for all patients continuing in the eye examination portion of the study.**

Signs and symptoms revealed and recorded during the PANSS, BARS, SAS, and AIMS rating should only be reported as AEs if they fulfill the criteria far a SAE or are the reason for discontinuation from treatment with the investigational product.

Individual protocol-mandated laboratory and other safety-related test results should not be recorded as AEs unless they fulfill the criteria for a SAE or lead to discontinuation of treatment with investigational product but will be evaluated in the overall safety analysis. If an abnormal laboratory or other safety-related test result is associated with clinical signs or symptoms, the sign or symptom should be recorded as an AE while the associated test result is recorded in the appropriate CRF section.

Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following criteria:

- results in death
- is immediately life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity

- is a congenital abnormality or birth defect

- is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

The causality of SAEs (i.e., their relationship to study drug) will be assessed by the investigator(s), who in completing the relevant case report form must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the drug?" For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol. **Serious adverse events will be collected for 30 days post study drug for all randomized patients. SAEs will be collected for all patients continuing in the eye examination portion of the study.**

Other significant adverse event (OAE)

The Clinical Study Team Physician will complete oAEs during the evaluation of the safety data for the Clinical Study Report who may consult the Drug Safety Physician if needed. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment, will be classified as OAEs. Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative will be written and included in the Clinical Study Report.

4.6.3.2 Recording of adverse events

Adverse events will be collected by means of a standard question (Have you had any health problems since the last visit?). The question will be asked to each patient at Visits 1 through 28. All Adverse events must be recorded in the case report forms provided.

The patient will be asked to provide a description of the event, the dates of onset and resolution, intensity of the event, action taken, and the outcome. To assess the intensity of the reported adverse event, the following scale will be used:

1. Mild: awareness of sign or symptom, but easily tolerated.

2. Moderate: discomfort sufficient to cause interference with normal activities.

3. Severe: incapacitating, with inability to perform normal activities.

The investigator should make a causality assessment of the relationship of the event to the study drug and whether it constitutes an SAE or not.

If a diagnosis of the patient's condition has been made, then the diagnosis should be recorded as the adverse event (e.g. fever, runny nose, cough can be recorded as "flu"). However, if a

diagnosis of the patient's condition has not been made, or only if the individual symptoms are not well recognized, then the individual symptoms should be recorded separately.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.6.3.1.An AE of severe intensity need not necessarily be considered serious. For example, nausea, which persists for several hours, may be considered severe nausea, but not a SAE. On the other hand, a stroke, which results in, only a limited degree of disability may be considered a mild stroke but would be a SAE.

For the purpose of this study, any detrimental change in a patient's condition subsequent to them entering the study should be considered to be an adverse event. When there is a deterioration in the condition for which the medicine is being used, there may be uncertainty as to whether this is lack of efficacy or an adverse event. In such cases, unless AstraZeneca or the reporting physician consider that the medicine contributed to the deterioration, or local regulations state to the contrary, the deterioration should be considered a lack of efficacy.

In general, abnormal laboratory test results or vital signs should not be reported as adverse events unless they fulfill the criteria for a serious adverse event or lead to discontinuation. If an abnormal laboratory test result or vital sign is associated with clinical signs and symptoms, the sign or symptom should be reported as an adverse event.

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 9.5. Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

4.6.3.3 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study **within 24 hours (1 day),** (i.e. immediately but no later than the end of the next business day) of when he or she becomes aware of it.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the AstraZeneca Drug Safety Department (i.e., Clintrace Data Entry Site) receives a report by **day one** for all fatal and life-threatening cases and by day five for all other SAEs.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca **within 24 hours (1 day)** as described above.

All SAEs have to be reported whether or not considered causally related to the investigational product. All SAEs will be recorded in the case report form. The investigator is responsible

for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

4.6.4 Laboratory safety measurements and variables

All clinical laboratory determinations will be performed by:

[redacted]

A local laboratory may be used to obtain immediate (Stat) reports if necessary.

4.6.4.1 Methods of assessment

4.6.4.2 [redacted] will provide all necessary documentation of licensure and normal ranges to AstraZeneca and the CRO. The following laboratory tests will be performed at screening and at the specified visit:

- The central laboratory will conduct a urine drug screen for investigator evaluation of substance abuse. The investigator will evaluate the toxicology results along with medical history to determine if the patient meets DSM-IV criteria for substance abuse. The following drugs will be captured in the drug screen: amphetamines, barbiturates, cocaine, methadone, methaqualone, opiates, phenothiazines, and propoxyphene. Patients with a positive urine drug screen (UDS) will have a repeat UDS within 7 to 21 days. If the UDS remains positive, with the exception of cannabinoids, the patient will be excluded. This test will be obtained at visit 1 (screening) only. It will be at the investigator's discretion to perform additional tests after visit 1.

- A urinalysis will be performed to determine the following concentrations at visit 1 (screening) and at completion or consent withdrawal:

  color
  specific gravity
  ketones
  pH
  glucose
  bilirubin
  protein
  red blood cells
  white blood cells
  blood
  microscopic

- Hematology (CBC w/differential & Total Absolute Neutrophils Count) tests will be performed at visit 1 (screening), monthly for the first three months, thereafter

quarterly (every 3 months) and at completion or consent withdrawal. The test will include the following:

white blood cell count - total and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
red blood cell count
hemoglobin
hematocrit
platelets
MCV

Absolute Neutrophils Count (if the patients ANC is <1.5 x10^9 / L, repeat test by next day. If ANC is still <1.5 x10^9 / L discontinue the patient from the study).

Monthly complete blood counts (CBC) with a white blood cells (WBC) differential count for the first three months and then quarterly thereafter, throughout the study.

A CBC with a WBC differential count on any patient who presents with a fever, pharyngitis, or other signs and symptoms of infection.

Instruct patients to seek medical care if they develop symptoms of infections such as fever and/or pharyngitis (sore throat) and mucous membrane ulceration.

If a patient has an absolute neutrophil count < 1.5 x10^9 / L, repeat the test within 24 hours. If it remains < 1.5 x10^9 / L, discontinue the drug.

Monitor these patients with a CBC and differential weekly until their counts recover. While experiencing neutropenia, patients should avoid invasive procedures such as dental work, rectal exams, or enemas; exposure to people who are obviously ill; and exposure to fresh fruits, vegetables, or flowers. If a patient develops fever or symptoms of infection, he/she should contact his/or her physician and acquire a CBC with differential immediately.

- Clinical chemistry tests will be performed at visit 1 (screening), quarterly (every 3 months), and at completion or consent withdrawal to determine the following concentrations:

  alanine aminotransferase (ALT)
  aspartate aminotransferase (AST)
  urea nitrogen
  creatinine
  sodium
  potassium
  total bilirubin
  alkaline phosphatase

albumin
glucose
GGT
uric Acid
calcium
phosphorus
total protein
insulin
bicarbonate
CK

- Prolactin levels will be obtained at visit 1 (screening) and at completion or consent withdrawal.

- Thyroid function tests will be performed at visit 1 (screening), quarterly (every 3 months), and at completion or consent withdrawal. The test will include the following:

  thyroid stimulating hormone (TSH)
  triiodothyronine resin uptake (T_3RU)
  total thyroxine (T_4)
  free thyroxine (FT_4)

- Hemoglobin A1c will be obtained at visit 1 (screening) and quarterly (every 3 months) and at completion or consent withdrawal.

- Lipid profile tests will be performed at visit 1 (screening), quarterly (every 3 months) and at completion or consent withdrawal. Labs will be conducted in a fasting state. The tests will include the following:

  high-density lipoprotein (HDL)
  low-density lipoprotein (LDL)
  triglycerides
  cholesterol

- Serum pregnancy test will be performed at visit 1 (screening), quarterly (every 3 months), and at completion or consent withdrawal. Serum pregnancy test may also be performed at the discretion of the principle investigator, when deemed clinically necessary.

- Vital signs/Weight (see Section 4.6.6)

- ECG will be performed at visit 1 (screening), every six months, and at completion or consent withdrawal.

Screening hematology with CBC and ANC, clinical chemistry, thyroid function test, lipid profile, glucose levels, and hemoglobin A1c must be conducted within 30 days of randomization (Day 1-Visit 2). If the interval between initial screening and randomization exceeds 30 days, the clinical laboratory tests must be repeated.

4.6.5 Other safety measurements and variables

To assess recognized side effects of antipsychotic agents the following psychiatric ratings will be performed by raters at the site to assess tolerability: Modified Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS).

4.6.5.1 SAS

The SAS is the sum of a 10-item scale that is used to rate the presence and intensity of extrapyramidal motor symptoms, with the score for each item ranging from 0 to 4. A rating of 9 indicates that the item cannot be scored. Increases from baseline in total score will indicate an increase in extrapyramidal motor symptoms.

4.6.5.2 BARS

The BARS has 4 items and is used to assess objective and Patientive attributes of akathisia. Only one item of the BARS, the Global Assessment of Akathisia, with a score ranging from 0 to 5 will be analyzed. Increases from baseline in the global assessment item score will indicate an increase in akathisia.

4.6.5.3 AIMS

The AIMS is the sum of a 10-item scale that is used to rate the presence and intensity of abnormal involuntary movements, with the score for each item ranging from 0 to 4. Increases from baseline in total score will indicate an increase in abnormal voluntary movements.

4.6.6 Vital Signs/Weight

Blood pressure, pulse, respiration rate, temperature, height and weight will be obtained at Visit 1 and completion or consent withdrawal. Blood pressure, pulse rate, temperature and weight will be obtained at all other visits. Blood pressure and pulse will always be obtained in both the supine and standing positions.

4.6.6.1 Methods of Assessment

An appropriately sized cuff will be used to obtain blood pressure in the supine and standing position. The method used at baseline should be used at subsequent visits. Weight should be measured (in kg) with the patient in light clothing, without shoes, and should be recorded using the same scale.

4.6.6.2 Calculation or derivation of outcome variables

Change from baseline in vital signs and weight will be derived as the value at the visit minus the value at randomization. Values outside the extended range will be flagged.

4.7 Collection of samples for genetic analysis

In addition to laboratory procedures outlined above, each patient will be asked if he or she is willing to donate a blood sample for genetic research. The analysis of these samples will be limited to genetic research aimed at identifying genetic polymorphisms that could influence susceptibility to schizophrenia or affect response (efficacy, safety, tolerability) to or disposition of the study drug (i.e., pharmacogenetics). DNA samples generated in this study will not be used as control samples for other types of genetic studies. In addition, these samples will not be used to study susceptibility to diseases other than (1) schizophrenia or (2) illnesses or adverse events that are not potentially related to study drug.

Consent for genetic testing will be obtained and documented through a form separate from that used for the main study. This form specifically states that sampling is optional and not a requirement for study participation. The DNA sampling element of this protocol is optional for investigational sites as well as for individual patients.

For patients who consent to genetic testing, an additional 10 ml of blood will be drawn, generally at the same time as the baseline blood sample. These samples will be stored at [redacted] and sent to a contract research laboratory for DNA extraction. The DNA samples, and the remainder of each blood sample, will then be forwarded to AstraZeneca.

The genetic samples (i.e., blood sample and the DNA extracted from it) from each participating patient will be recoded with a number that links it to similarly recoded clinical information. The genetic data derived from each sample will only be labeled with the second code number. A document that links the DNA sample's new code with its original code will be stored in a secure, restricted-access file (the "link file") at AstraZeneca. The purpose of recoding genetic samples and clinical data is to enhance confidentiality by providing an additional layer of separation between patient identity and genetic research results. The purpose of preserving the link file is threefold: (1) to allow regulatory authorities such as the Food and Drug Administration to track samples and ensure that research is being conducted properly; (2) in highly unusual circumstances, to allow access to genetic data by AstraZeneca drug safety physicians investigating serious adverse events, and (3) to allow for the location and destruction of relevant genetic samples in case a patient withdraws from the genetic research portion of this study. The link file will be destroyed 15 years after the completion of the study. AstraZeneca can only destroy the DNA sample while the link is maintained. AstraZeneca cannot destroy genetic data that has already been produced. All DNA samples from this study will be destroyed in 15 years, at the same time that the link file is destroyed.

If a patient withdraws consent for genetic research, the investigator at the study site should notify the AstraZeneca study physician or coordinator, who will then send a request for sample destruction to the head of the AstraZeneca Clinical Genotyping Group. The study site will receive written confirmation that the relevant genetic samples (i.e., DNA and any remaining blood) have been destroyed.

All genetic research results will be kept confidential in accordance with all applicable laws. Results that lack personal identifying information may be reviewed with research collaborators and published. Otherwise, no genetic test results will be made available to the patient; to any insurance company, employer, or family member; or to the investigator or any other present or future treating physician.

The results of any genetic research, and any genetic sequences, cell lines, patents, diagnostic tests, drugs, or biological products developed directly or indirectly as a result of this study, as well as any information derived directly or indirectly from those samples, are the sole property of the study sponsor (and its successors, licensees, and assignees) and may be used for commercial purposes. Participating patients have no right to this property or to any share of the profits that may be earned directly or indirectly as a result of this study.

4.8 Volume of blood sampling and handling of biological samples

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 10 Volume of blood to be drawn from each patient

Assessment	Sample volume (ml)	N of samples	Total volume (ml)
Full clinical chemistry (including thyroid, lipid panel, fasting glucose and prolactin)	12 (2-six ml tubes) *	11	120
Hematology (including hemoglobin A1c, CBC w/differential & Total Absolute Neutrophils Count) **	4	11	44
Fasting Serum Insulin* **	**4**	**11**	**44**
Genotyping	10	1	10
Total** **			30 ml (screening) 20 ml (quarterly and completion) 14 ml for all other visits 218 ml (total)

*One 6 ml clinical chemistry sample will be for the thyroid panel and serum prolactin and serum beta HCG. The other 6 ml tube will be for chemistry, lipid, and fasting glucose. Two 6ml will be collected at screening, quarterly, and completion and two 6ml at all other visits

** The hemoglobin A1c**,** CBC w/differential and absolute neutrophil count will be taken from the hematology sample. Hematology with differential and absolute neutrophil count will be collected at visit 1 (screening) monthly for the first three months, thereafter quarterly (every 3 months), and at completion or consent withdrawal (11). Hemoglobin A1c will be collected at the baseline, quarterly, and completion visits; or upon consent withdrawal (9).

***Sample must be frozen.

****Additional samples may be required for retests.

The blood samples for genetic research should be collected in a 10 ml polypropylene tube (Becton-Dickson Vacutainer K2E, 10 ml), and gently inverted several times. Samples should be shipped to [redacted]. The samples should contain only the patient enrollment number (E code) and date of collection, and no personal identifying information.

Sample handling and processing will be coordinated through the Development Pharmacogenetics and Clinical Genotyping Groups, Alderley Park, UK. Detailed instructions on sample handling and shipment will be supplied in additional documentation.

In all cases, once collected samples should be stored at +4°C (fridge) if shipment is to be within 24 hours of sampling or frozen at -20°C or colder if shipment is to be more than 24 hours after sampling. For samples shipped within 24 hours of collection shipment at ambient temperature will suffice. Samples that have been frozen should not be thawed, but should be sent frozen on dry ice to ensure that they remain frozen in transit. Where possible samples should be shipped in batches and shipment coordinated with the receiving site to ensure that samples arrive within working hours, on normal working days (i.e. avoiding delivery on weekends, holidays, etc.). A requisition sheet detailing protocol number, sample patient enrollment number (E code), date of collection and confirmation of informed consent for every sample should accompany the sample shipment.

5. DATA MANAGEMENT

Case report forms (CRFs) will be provided for the recording of data. The forms will be in triplicate with carbonless paper. Data will be recorded legibly onto the record forms, preferably in black ballpoint pen. If any data are not available, omissions will be indicated on the recorded forms. Corrections should be made legibly and initialed and dated. Correction fluid or covering labels must not be used. The top original and the 1st copy of the completed form will be collected and returned to AstraZeneca or its designee and the investigator will retain the remaining copies.

The ophthalmologist site will record the patient's slit lamp assessments by the two ophthalmologists into an IVRS system that will serve as the database for the study.

CRO will enter the data into their database and carry out data validation by an agreed process between the CRO and AstraZeneca. Any data queries following validation will be raised via data query sheets or the CRO equivalent. Approved personnel who will sign and date the query resolution will deal with these queries at the investigator site. Resolved queries will be returned to the CRO and, where necessary, the database updated accordingly.

At agreed times during the study and at the end, data will be transferred from the CRO to AstraZeneca in a format to be agreed with the CRO.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

A comprehensive Statistical Analysis Plan (SAP) will be prepared before first patient is enrolled in the study.

6.1.1 Methods of statistical analysis

The Quantitative Decision Sciences Department, AstraZeneca Pharmaceuticals LP, will be responsible for performing the analyses and creating tables, listings, and figures. Validated statistical software will be used to conduct all analyses.

The primary objective of the evaluation of the cataractogenic potential of quetiapine is to demonstrate statistically that the proportions of cataractogenic events in quetiapine-treated patients are not higher to a clinically meaningful degree than the proportions of events in risperidone-treated patients.

6.1.2 Populations for analysis

The primary analyses of the endpoints will be based on per protocol (PP) populations.

PP will be defined for the analysis as those patients who have completed at least 21 months of treatment or experienced an event at an earlier slit lamp examination and withdrew, without a significant protocol violation or deviation. A significant protocol violation or deviation is defined as an event that interferes with the primary objective of this study, which is to compare the cataractogenic potential of 2 antipsychotic drug treatments. Examples of such events include ocular trauma, ocular surgery, use of medications excluded at baseline (e.g. steroids, psoralens, allopurinol). For the PP analysis, data will be analyzed according to the treatment given to the patients.

An intent to treat (ITT) population will be used for secondary analyses. This will include all patients who received treatment and had at least one post baseline slit lamp examination. Every attempt will be made to continue the ITT patients through the 2 years examination for the eye examinations and slit lamp assessments. The ITT analysis will be performed on patients as randomized, including those followed with slit lamp exams after treatment withdrawal.

There will also be a safety population defined as any patient who actually took any study drug, according to the treatment actually taken for assessment of EPS adverse events, adverse events, clinical laboratory assessments, vital signs, electrocardiograms, BARS, SAS, AIMS.

6.1.3 Study variables

Primary variables:

Presence/absence of cataractogenic events in patients with 2 years of exposure (minimum of 21 months) including patients withdrawn for an event. Events of N, C or P as agreed by 2 independent treatment masked non-consulting ophthalmologists at the 24-month visit or earlier for patients who withdrew due to the event.

Secondary variables:

Incidence, severity and causality of EPS, adverse events, OAEs, SAEs and withdrawals due to adverse events.

Changes in vital signs, clinical laboratory assessments, physical examination, and ECGs from baseline to each assessment visit.

Investigator rating scales for extrapyramidal effects: SAS, BARS and AIMS from baseline to final assessment.

Efficacy variables will include: PANSS total score, PANSS positive subscale score, PANSS negative subscale score, PANSS psychopathology subscale score, CGI Severity of Illness score, CGI Global Improvement, time to first relapse of schizophrenia or schizoaffective disorder, and number of relapses of schizophrenia or schizoaffective disorder.

Patient reported outcomes will include: QLESSF and PETiT.

Safety outcome variable will include: Findings of worsening of visual acuity (at least 2 line deterioration) in Snellen Eye Chart assessment in patients with and without cataractogenic events at study endpoint or patient discontinuation/termination.

6.1.4 Statistical analysis

6.1.4.1 Cataractogenic Potential Analyses

Hypotheses: Testing of 3 simultaneous non-inferiority hypotheses:

H_o: $P_i(S) - P_i(R) >= \Delta_i$, for any i=N, C, P H_a: $P_i(S) - P_i(R) < \Delta_i$, for all i= N, C, P.

The primary analyses of the evaluation of cataractogenic potential will compare between randomized treatment groups the proportions of evaluable patients with a specific cataractogenic event (N, C or P) as assessed by 2 independent non-consulting ophthalmologists at the 24-month visit. This primary evaluable patient group will be the PP population. Exact two-sided 95% confidence intervals for the differences in proportions between the quetiapine and risperidone treated groups will be calculated for the rates of N, C and P events. If none of these 3 upper 95% confidence limits exceeds the predefined non-inferiority limit (10%), we will conclude that the event rate in the quetiapine-treated patients is not higher to a clinically meaningful degree than the rate in the risperidone-treated patients.

The evaluation of the difference between 2 binomials would be calculated for each event (P, C, N) and an exact method used to calculate the CI.

6.1.4.2 Supportive Analysis for Cataractogenic Potential

In addition to the primary analysis of cataractogenic potential, a number of supportive secondary eye analyses will be conducted including the following: An intention to treat population analysis of cataractogenic potential using the model defined in Section 6.1.4.1, but incorporating slit lamp evaluations subsequent to discontinuation of study medication for patients with less than 21 months of study medication exposure.

An analysis of time to detectable cataractogenic event. Kaplan-Meyers survival analysis will be used for the time to cataractogenic event data; survival time will be censored at the time of withdrawal for patients withdrawing prior to the occurrence of an event. Kaplan-Meyers survival curve plot will be generated to graphically support the analysis. A Cox proportional hazard model will also be used to evaluate treatment differences in time to cataractogenic event.

In patients with cataractogenic events, the visual acuity via a Snellen Eye Chart will be assessed, and change from baseline tabulated using descriptive statistics.

Sensitivity analysis using logistic regression to evaluate the impact of possible explanatory variables (including but not limited to previous treatment exposure, duration of exposure, age, sex, concomitant medications, etc.) on the rate of cataractogenic events. The consideration of these explanatory variables will be regarded as exploratory and a variable will be retained in the model if it reaches the 0.05 level of significance.

6.1.4.3 Other Data Summarization's

All demographic data, medical history, surgical history, details of physical examinations and concurrent medications taken will be summarized using appropriate descriptive statistics (e.g. mean, median, standard deviation, range for numerical data and frequencies for categorical data).

Secondary Analysis:

Number of and crude incidence rates for adverse events in each treatment group will be summarized using MEDRA terminology. An event which occurs one or more times on the date of or subsequent to randomization will contribute one observation to the numerator of the crude incidence rate; all patients exposed to treatment will comprise the denominator of the rate.

Treatment group will tabulate adverse events, which lead to premature withdrawal of patients from the study. The intensities of all adverse events will also be tabulated for each treatment group.

All laboratory safety data as well as vital signs data will be summarized using standard summary statistics by treatment group and by visit. Clinical laboratory results and vital signs will be summarized as change from baseline. Treatment group will separate these summaries. Categorical summaries of ECG data will also be produced and displayed by treatment group. Treatment group will also summarize clinically significant abnormalities with respect to physical examination. No formal statistical analyses will be made on these safety data.

Assessment of tolerability using SAS, BARS, and AIMS will be summarized using standard descriptive statistics by treatment group and visit and comparisons between treatments will be performed using analysis of variance with the baseline assessment as a covariate in the model.

Absolute values and changes from baseline over time in CGI (severity and improvement), PANSS (total, positive, negative, general psychopathology), QLESSF and PETiT will be summarized using standard descriptive summary statistics by treatment group and by visit.

Time to first relapse will be assessed descriptively using Kaplan-Meyers curves.

6.2 Description of outcome variables in relation to objectives and hypotheses

Description of N, C or P event. (See Section 4.6.2.2)

Description of relapse. (see Section 4.5.7)

6.3 Description of analysis sets

The LOCS II analysis data set will include a variable for presence or absence of an event derived from the results of the slit lamp evaluation by 2 independent non-consulting ophthalmologists. This will include a binomial response from each eye and type opacity; N, C and P (1=present, 0=absent) for both agreement and disagreement at the eye assessment. For patients who withdraw early because of a cataract event, the resulting event from the patient's final assessment is carried forward to the 2-year final assessment.

For each efficacy, quality of life, and tolerability scale data set the analysis data set will include the item scores, a total score and any appropriate derived subscale score and for each score there will also be a variable for the associated change from baseline.

The adverse event data will include the information from the adverse event form and derived onset in relation to start of treatment, dose at onset of event and derived duration of event.

Laboratory analysis data sets will have the value, change from baseline derived, flag for outside of normal range, and flag for value outside the critical levels defined for the study.

6.4 Method of statistical analysis

This will be described in detail in the SAP.

6.5 Determination of sample size for cataractogenic potential

Sample size estimation is based on the simultaneous testing of 3 non-inferiority hypotheses:

H_o: $P_i(S) - P_i(R) >= \Delta_i$, for any i=N, C, P

H_a: $P_i(S) - P_i(R) < \Delta_i$, for all i= N, C, P

With 170 evaluable patients per group, as Table 8 shows, the power to reject all 3 null hypotheses would be at the least 86% assuming all three events are at 7% (i.e. .95*.95*.95). The published literature would suggest that an assumed event rate of 7% is high; thus the power to reject all 3 null hypotheses is conservative.

Table 11 Power of a single non-inferiority test with 170 evaluable patients per treatment group

Event rate[a]	**Non-inferiority limit (Δ)**[b]	**Power** [c]
5%	**10%**	**98%**
6%	**10%**	**97%**
7%	**10%**	**95%**

[a] The underlying event rates in the quetiapine-treated group $P_i(S)$ and the control group $P_i(R)$ are assumed to be equal.
[b] Delta is defined as the difference in event rates between the quetiapine-treated group and the control group.
[c] Power was calculated assuming an alpha=.025 1-sided test.

Assuming 40% of patients will complete at least 21 months of treatment without significant protocol violations or deviations, 535 patients randomized into the quetiapine group and 465 patients randomized into the risperidone treatment group will be necessary to obtain 170 evaluable patients per treatment group. To account for an expected 5% drop out rate before the 6-month slit lamp examination (replaced) and 10% rate of unevaluable patients due to protocol violations and deviations, approximately 535 quetiapine patients and 465 risperidone patients will be randomized. The overall power of the study is approximated by the product of powers of the 3 individual tests.

According to the literature, the incidence of cortical opacification at 2 years ranges from 4% to 5% (Laites 1991 grading based like LOCS II, Leske 1997 LOCS III, Leske 2000 LOCS II). The incidence of posterior subcapsular opacification at 2 years in the literature ranges from 1.3% to 6.8% (Laites 1991, Leske 1997, Leske 2000). The incidence of nuclear opalescence at 2 years ranges from 0% to 5.8% in the literature (Laites 1991, Leske 1996 LOCS III, Leske 2000, Lyle 1999 different grading system Am J Clin Nutr, Lyle 1999 different grading system Am J Epi).

The non-inferiority limits for comparisons of P, C and N event rates have been set at 10% in consultation with the FDA.

The completion rate will be monitored throughout the study to assure that the 170 evaluable patients are obtained. In addition, dose and cataractogenic events will also be monitored throughout the study to assess safety.

6.6 Interim analyses

No statistical interim analyses will be performed. Ongoing safety monitoring will be conducted.

6.7 Data and safety monitoring board

An independent board of 3 experts in cataracts will meet with AstraZeneca study personnel on a quarterly basis to scientifically and medically review all events. This board will determine whether there are unusual or unexpected trends in the number or type of events recorded with either or both study medications, which may necessitate termination of all or part of the trial for safety purposes. They may also assist in recommendations for additional LOCS II training for specific ophthalmologic sites, if their data appears discordant from others.

7. STUDY MANAGEMENT

7.1 Monitoring

Before the first patient enters the study, a representative of AstraZeneca or the CRO will visit the psychiatric and ophthalmologic investigational sites to:

- determine the adequacy of the facilities
- discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement (CSA) between AstraZeneca and the investigator.
- ensure that the investigator and other personnel at the study site are familiar with the optional consent for genetic research and with applicable privacy regulations.

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the investigational site, including visits to:

- provide information and support to the investigator(s)
- confirm that facilities remain acceptable
- confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms (CRFs), and that investigational product accountability checks are being performed

- perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each patient (e.g., clinic charts).

The monitor or another AstraZeneca representative will be available between visits if the investigator(s) or other staff at the center need information and advice.

7.2 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the center to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The investigator should contact AstraZeneca or the CRO immediately if contacted by a regulatory agency about an inspection at his or her center.

7.3 Training of staff

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

7.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the Coordinating Investigator and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (Amended Protocol) must be approved by each IEC or IRB, and if applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If a protocol amendment requires a change to a particular center's Written Informed Consent Form, then AstraZeneca, the CRO and the center's IEC or IRB must be notified. Approval of the revised Written Informed Consent Form by AstraZeneca, the CRO and by the IEC or IRB is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to each principal investigator(s), who in turn is responsible for the distribution of these documents to his or her IEC or IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

7.5 Study agreements

The principal investigator at each center must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

7.6 Study timetable and termination

Before a patient's enrollment in the study and any study-related procedures are undertaken the following should be fulfilled:

- signed Clinical Study Protocol and other agreements between AstraZeneca and the Principal Investigator/Study Site.
- written approval of the study by the IRB/IEC.
- written approval of the study, if applicable, by the regulatory authority.
- signed Form FDA 1572 by the Principal Investigator.

Planned duration of the study

Estimated date of first Patient enrolled: [redacted]

Estimated date of last Patient completed: [redacted]

Estimated recruitment period: [redacted]

Discontinuation or suspension of the whole study program

If AstraZeneca decides to withdraw or suspend the study, the principal investigator/sub-investigator, the head of the institution, and regulatory authorities should be informed of the fact in a written form clarifying the reason.

The principal investigator/sub-investigator will immediately notify the patients of the decision, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

Completion of the study

Upon terminating the study, the principal investigator/sub-investigator will report in writing the completion of the study as well as the summary of the results to the head of the institution in accordance with the institution's rules. The head of the institution who is informed of the termination by the investigator will notify in writing the fact with the summarized results to the IRB and AstraZeneca.

8. ETHICS

8.1 Ethics review

The final study protocol, including the final version of the Written Informed Consent Form, must be approved or given a favorable opinion in writing by an IEC or IRB as appropriate. The investigator must submit written approval to AstraZeneca or AstraZeneca's representative before he or she can enroll any patient into the study.

The principal investigator(s) is responsible for informing the IEC or IRB of any amendment to the protocol in accordance with local requirements. In addition, the IEC or IRB must approve all advertising used to recruit patients for the study. The protocol must be reapproved by the IEC or IRB annually, as local regulations require.

Progress reports and notifications of serious unexpected drug reactions will be provided to the IEC or IRB according to local regulations and guidelines. The principal investigator(s) must also provide the IEC or IRB with any reports of serious adverse events from the study site.

The principal investigator(s) is also responsible for providing the IRB with reports of any serious adverse events from any other study conducted with the investigational product. AstraZeneca will provide this information to the principal investigator(s).

8.2 Ethical conduct of the study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki (see Appendix H) and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

In addition, AstraZeneca ensures that special precautions are taken for studies including genetic analysis, with regard to the process for ensuring confidentiality of data.

8.3 Written informed consent

The principal investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any procedure specifically for the study, including the following:

- withholding or discontinuation of treatment
- collection of blood samples
- Completion of rating scales and questionnaires

- physical examination

The principal investigator(s) must store the original, signed Written Informed Consent Form. A copy of the Written Informed Consent Form must be given to the patient.

Where genetic analyses are included, special account of these will be made in the consent form, as it is recognized that special provisions need to be made to retain confidentiality of medical information. These factors have been taken into account in the design of the consent form. Consent forms specific for giving consent for taking samples for genotyping will be used, the format depending on the design of the study. The patient's signed and dated informed consent(s) must be obtained before conducting any procedure specifically for the study. The principal investigator(s) must store the original, signed Written Informed Consent Form(s). A copy of the signed Written Informed Consent Form(s) must be given to the patient.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

8.4 Patient data protection

AstraZeneca recognizes the importance of protecting the privacy of patient (patient) data. Therefore, for study sites within the US or in studies where foreign patients' protected health information (patient data) will come into the US through a covered entity (e.g., Central Lab/Reader), the Informed Consent Form will incorporate, or be accompanied by, a separate document incorporating HIPAA-compliant wording by which patients authorize the use and disclosure of their Protected Health Information by the Investigator and by those persons who need that information for the purposes of the study.

The Written Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by patient number, study code and patient initials.

The Written Informed Consent Form will also explain that for data verification purposes, authorized representatives of AstraZeneca, a regulatory authority, an IEC or IRB may require direct access to parts of the hospital or practice records relevant to the study, including patient's medical history.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. This involves de-identification/anonymization of the samples and data. For de-identification this will mean that there is segregation of the databases containing coded genotypic and clinical information with protection of confidentiality achieved by limited access to the coding keys of each database. (Details of the procedure specific to this study are in Section 5).

9. EMERGENCY PROCEDURES

9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency, contact the Clinical Study Team Leader. If the Clinical Study Team Leader is not available, contact the Clinical Study Physician at the AstraZeneca Research and Development site shown below.

Role in the study	Name	Address and telephone number
Clinical Study Team Leader	[redacted]	[redacted]
Clinical Study Physician	[redacted]	[redacted]

CRO Contact Information		
Role in the study	**Name**	**Address and telephone number**
Project Manager	[redacted]	[redacted]
Clinical Lead	[redacted]	[redacted]
Medical Advisor	[redacted]	[redacted]
The local AstraZeneca representative could be found on page 2 in this protocol, AstraZeneca emergency contact procedure		

Contact AstraZeneca switchboard at [redacted] and ask to be put in contact with the SEROQUEL clinical team.

9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study.

9.3 Procedures in case of overdose

For the purpose of this study, an overdose for quetiapine will be any dose greater than 800 mg, and for risperidone it will any dose greater than 16 mg, all overdoses with or without associated symptoms should be reported as adverse events. This also includes self-administration by the patient of a dose greater than 800 mg for quetiapine and 16 mg for risperidone. However, all cases of overdose must be reported immediately, **within 1 day**, if sequelae meeting the criteria for serious adverse event have occurred in association with the

overdose. In all instances, the overdose substance should be stated and an assessment of whether the overdose was accidental or intentional should be recorded. If the overdose was a suicide attempt, this fact should be clearly stated. Adverse events (serious and non-serious) that occur as the result of an overdose should be recorded on the Adverse Event CRF as "sequelae to overdose". For example, "nausea as sequelae to overdose".

All overdoses, with or without associated symptoms, should be reported as AEs or SAEs in accordance with the following procedure:

- An Overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the CRF.
- An Overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the CRF and the Overdose should be reported on the separate AZ "Clinical Study Overdose Report Form."
- An Overdose without associated symptoms should not be recorded as an AE in the CRF. The Overdose should be reported on the separate AZ "Clinical Study Overdose Report Form".

9.4 Suicide

Suicide and suicide attempt, irrespective of the method, but in connection with the use of study drug, should be reported as a serious adverse event (in accordance with the definition provided in Section 4.6.3.1. This event should be identified as a suicide or suicide attempt, and the method of the suicide or the suicide attempt should be provided.

9.5 Procedures in case of pregnancy

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report form.

10. REFERENCES

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AstraZeneca

Clinical Study Protocol: Appendix A

Drug Substance	quetiapine fumarate
Study Code	5077IL/0089
Edition No.	1
Appendix Date	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

Study Title

A multicenter, open-label, flexible-dose, parallel-group evaluation of the cataractogenic potential of quetiapine fumarate (SEROQUEL™) and risperidone (RISPERDAL™) in the long-term treatment of patients with schizophrenia or schizoaffective disorder

I agree to the terms of this study protocol

AstraZeneca Research and Development site representative

[redacted]

Date
(Day Month Year)

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

ASTRAZENECA SIGNATURE(S)

Study Title

A multicenter, open-label, flexible-dose, parallel-group evaluation of the cataractogenic potential of quetiapine fumarate (SEROQUEL™) and risperidone (RISPERDAL™) in the long-term treatment of patients with schizophrenia or schizoaffective disorder

I agree to the terms of this study protocol

AstraZeneca Research and Development site representative

[redacted]

Date
(Day Month Year)

ASTRAZENECA SIGNATURE(S)

Study Title

A multicenter, open-label, flexible-dose, parallel-group evaluation of the cataractogenic potential of quetiapine fumarate (SEROQUEL™) and risperidone (RISPERDAL™) in the long-term treatment of patients with schizophrenia or schizoaffective disorder

I agree to the terms of this study protocol

AstraZeneca Research and Development site representative

<<Name, title>> Local Study Team <<Leader/Monitor/ Physician, *According to local procedures>>* *<<Address and telephone number>>*	Date (Day Month Year)

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

SIGNATURE OF PRINCIPAL INVESTIGATOR

Study Title

A multicenter, open-label, flexible-dose, parallel-group evaluation of the cataractogenic potential of quetiapine fumarate (SEROQUEL™) and risperidone (RISPERDAL™) in the long-term treatment of patients with schizophrenia or schizoaffective disorder

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Centre No.: *<<This may be hand-written onto the page at the time the signature is collected>>*

Signature:

<<Name, title, address and telephone number>>

Date
(Day Month Year)

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

SIGNATURES OF COMMITTEE MEMBERS

Study Title

A multicenter, open-label, flexible-dose, parallel-group evaluation of the cataractogenic potential of quetiapine fumarate (SEROQUEL™) and risperidone (RISPERDAL™) in the long-term treatment of patients with schizophrenia or schizoaffective disorder

We agree to the terms of this study protocol. We will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Committee: *<<Insert name of the committee here, eg, "Endpoint Committee", "Safety Committee". If there is more than one committee, use a separate signature page for each committee>>*

Members signature:

<<Name, title/position and address>>	Date (Day Month Year)
<<Name, title/position and address>>	Date (Day Month Year)
<<Name, title/position and address>>	Date (Day Month Year)
<<Name, title/position and address>>	Date (Day Month Year)

AstraZeneca

Clinical Study Protocol: Appendix B	
Drug Substance	quetiapine fumarate
Study Code	5077IL/0089
Edition No.	1
Appendix Date	

Appendix B
Additional Safety Information

1. FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g. hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg. bronchospasm, laryngeal, edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Examples of such events are:

- *Angioedema not severe enough to require intubation but requiring iv. hydrocortisone treatment*
- *Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine*
- *Intensive treatment in an emergency room or at home for allergic bronchospasm*
- *Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization*
- *Development of drug dependency or drug abuse*

2. A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A “reasonable possibility” could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

AstraZeneca

Clinical Study Protocol: Appendix C	
Drug Substance	quetiapine fumarate
Study Code	5077IL/0089
Edition No.	1
Appendix Date	

Appendix C
DSM-IV Criteria for Selected Psychiatric Disorders

1. DIAGNOSTIC CRITERIA FOR SCHIZOPHRENIA

(A) Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

(1) delusions

(2) hallucinations

(3) disorganized speech (e.g., frequent derailment or incoherence)

(4) grossly disorganized or catatonic behavior

(5) negative symptoms, i.e., affective flattening, alogia, or avolition

Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

(B) Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbances, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

(C) Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or leas if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

(D) Schizoaffective and Mood Disorder exclusion: Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

(E) Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

(F) Relationship to a Pervasive Developmental Disorder: If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Classification of longitudinal course (can be applied only after at least 1 year has elapsed since the initial onset of active-phase symptoms):

Episodic With Interepisode Residual Symptoms (episodes are defined by the re-emergence of prominent psychotic symptoms); also specify if: **With Prominent Negative Symptoms**

Episodic With No Interepisode Residual Symptoms

Continuous (prominent psychotic symptoms are present throughout the period of observation); also specify if: **With Prominent Negative Symptoms**

Single Episode In Partial Remission; also specify if: **With Prominent Negative Symptoms**

Single Episode In Full Remission

Other or Unspecified Pattern

2. DIAGNOSTIC CRITERIA FOR 295.20 CATATONIC TYPE

A type of Schizophrenia in which the clinical picture is dominated by at least two of the following:

(1) motoric immobility as evidenced by catalepsy (including waxy flexibility) or stupor

(2) excessive motor activity (that is apparently purposeless and not influenced by external stimuli)

(3) extreme negativism (an apparently motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism

(4) peculiarities of voluntary movement as evidenced by posturing (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, prominent mannerisms, or prominent grimacing

(5) echolalia or echopraxia

3. DIAGNOSTIC CRITERIA FOR 295.10 DISORGANIZED TYPE

A type of Schizophrenia in which the following criteria are met:

All of the following are prominent:

A. All of the following are prominent:

(1) disorganized speech

(2) disorganized behavior

(3) flat or inappropriate affect

B. The criteria are not met for Catatonic Type

4. DIAGNOSTIC CRITERIA FOR 295.30 PARANOID TYPE

A type of Schizophrenia in which the following criteria are met:

A. Preoccupation with one or more delusions or frequent auditory hallucinations.

B. None of the following is prominent: disorganized speed, disorganized or catatonic behavior, or flat or inappropriate affect.

5. DIAGNOSTIC CRITERIA FOR 295.90 UNDIFFERENTIATED TYPE

A type of Schizophrenia in which symptoms that meet Criterion A are present, but the criteria are not met for the Paranoid, Disorganized, or Catatonic Type.

6. DIAGNOSTIC CRITERIA FOR 295.60 RESIDUAL TYPE

A type of Schizophrenia in which the following criteria are met:

A. Absence of prominent delusions, hallucinations, disorganized speech, and grossly disorganized or catatonic behavior.

B. There is continuing evidence of the disturbance, as indicated by the presence of negative symptoms or two or more symptoms listed in Criterion A for Schizophrenia, present in attenuated form (e.g., odd beliefs, unusual perceptual experiences).

7. DIAGNOSTIC CRITERIA FOR 295.70 SCHIZOAFFECTIVE DISORDER

A. An uninterrupted period of illness during which, at some time, there is either a Major Depressive Episode, a Manic Episode, or a Mixed Episode concurrent with symptoms that meet Criterion A for Schizophrenia.

Note: The Major Depressive Episode must include Criterion A1: depressed mood.

B. During the same period of illness, there have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms.

C. Symptoms that meet criteria for mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness.

D. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify type:

Bipolar Type: If the disturbance includes a Manic or a Mixed Episode (or a Manic or Mixed Episode and Major Depressive Episodes)

Depressive Type: If the disturbance only includes Major Depressive Episodes

AstraZeneca

Clinical Study Protocol: Appendix D	
Drug Substance	quetiapine fumarate
Study Code	5077IL/0089
Edition No.	1
Appendix Date	

Appendix D
DSM-IV Diagnostic Criteria for Substance Abuse

1. CRITERIA FOR SUBSTANCE ABUSE

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

(1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)

(2) recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)

(3) recurrent substance-related legal problems (e.g., arrests for substance –related disorderly conduct)

(4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

B. The symptoms have never met the criteria for Substance Dependence for this class of substance.

AstraZeneca

Clinical Study Protocol: Appendix E	
Drug Substance	quetiapine fumarate
Study Code	5077IL/0089
Edition No.	1
Appendix Date	

Appendix E
Potent Cytochrome P450 3A4 Inducers and Inhibitors

POTENT CYTOCHROME P450 3A4 INDUCERS AND INHIBITORS

Inhibitors

ketoconazole
itraconazole
clarithromycin
erythromycin
fluvoxamine
nefazodone

Inducers

barbiturates
carbamazepine
phenytoin
rifabutin
rifampin
St. John's Wort

Thioridazine should also be avoided. There are a few protease inhibitors and NNRTIs that AIDS patients would be on which should be discussed with AstraZeneca prior to use.

Clinical Study Protocol: Appendix F	
Drug substance:	quetiapine fumarate
Study Code:	5077IL/0089
Appendix Edition No:	1
Appendix Date:	

Appendix F
Seroquel Package Insert

SEROQUEL®

(quetiapine fumarate)

TABLETS

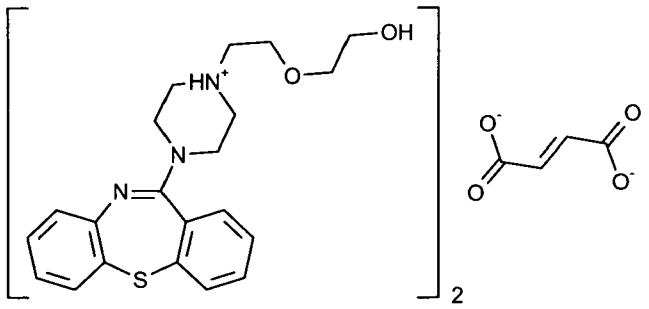
Rx only

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. SEROQUEL (quetiapine) is not approved for the treatment of patients with Dementia-Related Psychosis.

DESCRIPTION

SEROQUEL® (quetiapine fumarate) is a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo *[b,f]* [1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL is supplied for oral administration as 25 mg (round, peach), 100 mg (round, yellow), 200 mg (round, white) and 300 mg (capsule-shaped, white) tablets.

Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg tablets contain only yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT_{1A}$ and $5HT_2$ (IC_{50s}=717 & 148nM respectively), dopamine D_1 and D_2 (IC_{50s}=1268 & 329nM respectively), histamine H_1 (IC_{50}=30nM), and adrenergic α_1 and α_2 receptors (IC_{50s}=94 & 271nM, respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM).

The mechanism of action of SEROQUEL, as with other drugs having efficacy in the treatment of schizophrenia and acute manic episodes associated with bipolar disorder, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than

dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of SEROQUEL.

SEROQUEL's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

SEROQUEL's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively.

Distribution: Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination: Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and

20% of the dose was recovered in the urine and feces, respectively.

Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite.

Population Subgroups:

Age: Oral clearance of quetiapine was reduced by 40% in elderly patients (≥ 65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary (See **DOSAGE AND ADMINISTRATION**).

Gender: There is no gender effect on the pharmacokinetics of quetiapine.

Race: There is no race effect on the pharmacokinetics of quetiapine.

Smoking: Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency: Patients with severe renal impairment (Clcr=10-30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency: Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In two of the 8 hepatically impaired patients, AUC and C_{max} were 3-times higher than those observed typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels

are expected in the hepatically impaired population, and dosage adjustment may be needed (See **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions: *In vitro* enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6 and 3A4.

Quetiapine oral clearance is increased by the prototype cytochrome P450 3A4 inducer, phenytoin, and decreased by the prototype cytochrome P450 3A4 inhibitor, ketoconazole. Dose adjustment of quetiapine will be necessary if it is coadministered with phenytoin or ketoconazole (See **Drug Interactions** under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam (See **Drug Interactions** under **PRECAUTIONS**).

Clinical Efficacy Data

Bipolar Mania

The efficacy of SEROQUEL in the treatment of acute manic episodes was established in 3 placebo-controlled trials in patients who met DSM-IV criteria for Bipolar I disorder with manic episodes. These trials included patients with or without psychotic features and excluded patients with rapid cycling and mixed episodes. Of these trials, 2 were monotherapy (12 weeks) and 1 was adjunct therapy (3 weeks) to either lithium or divalproex. Key outcomes in these trials were change from baseline in the Young Mania Rating Scale (YMRS) score at 3 and 12 weeks for monotherapy and at 3 weeks for adjunct therapy. Adjunct therapy is defined as the simultaneous initiation or subsequent administration of SEROQUEL with lithium or divalproex.

The primary rating instrument used for assessing manic symptoms in these trials was YMRS, an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score).

The results of the trials follow:

Monotherapy

In two 12-week trials (n=300, n=299) comparing SEROQUEL to placebo, SEROQUEL was superior to placebo in the reduction of the YMRS total score at weeks 3 and 12. The majority of patients in these trials taking SEROQUEL were dosed in a range between 400 and 800 mg per day.

Adjunct Therapy

In this 3-week placebo-controlled trial, 170 patients with acute bipolar mania (YMRS $\geq$ 20) were randomized to receive SEROQUEL or placebo as adjunct treatment to lithium or divalproex. Patients may or may not have received an adequate treatment course of lithium or divalproex prior to randomization. SEROQUEL was superior to placebo when added to lithium or divalproex alone in the reduction of YMRS total score.

The majority of patients in this trial taking SEROQUEL were dosed in a range between 400 and 800 mg per day. In a similarly designed trial (n=200), SEROQUEL was associated with an improvement in YMRS scores but did not demonstrate superiority to placebo, possibly due to a higher placebo effect.

Schizophrenia

The efficacy of SEROQUEL in the treatment of schizophrenia was established in 3 short-term (6-week) controlled trials of inpatients with schizophrenia who met

DSM III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600 and 750 mg/day on a tid schedule), the 4 highest doses of SEROQUEL were generally superior to placebo on the BPRS total score, the BPRS psychosis cluster and the CGI severity score, with the maximal effect seen at 300 mg/day, and the effects of doses of 150 to 750 mg/day were generally indistinguishable. SEROQUEL, at a dose of 300 mg/day, was superior to placebo on the SANS.

(2) In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a tid schedule) and low (up to 250 mg/day on a tid schedule) doses, only the high dose SEROQUEL group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and the SANS.

(3) In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day on both bid and tid schedules and 50 mg/day on a bid schedule), only the 450 mg/day (225 mg bid schedule) dose group was generally superior to the 50 mg/day (25 mg bid) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS.

Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 compared to those older than 40. The clinical significance of this finding is unknown.

INDICATIONS AND USAGE

Bipolar Mania

SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex.

The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania (See **CLINICAL PHARMACOLOGY**). Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunct therapy. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION**).

Schizophrenia

SEROQUEL is indicated for the treatment of schizophrenia.

The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients (See **CLINICAL PHARMACOLOGY**).

The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. SEROQUEL (quetiapine) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning).

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the

syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General:

Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially

during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (23/2567) of the patients treated with SEROQUEL, compared with 0% (0/607) on placebo and about 0.4% (2/527) on active control drugs.

SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid (See **DOSAGE AND ADMINISTRATION**). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

Cataracts: **The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.**

Seizures: During clinical trials, seizures occurred in 0.6% (18/2792) of patients treated with SEROQUEL compared to 0.2% (1/ 607) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free

thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (12/2791) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where SEROQUEL was added to lithium or divalproate, 12% (24/196) of SEROQUEL treated patients compared to 7% (15/203) of placebo treated patients had elevated TSH levels. Of the SEROQUEL treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels.

Cholesterol and Triglyceride Elevations: In schizophrenia trials, SEROQUEL treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL treated patients.

Hyperprolactinemia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see **Carcinogenesis**). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of

drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Transaminase Elevations: Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROQUEL and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Priapism: One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may

share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation: Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses (see Renal Impairment and Hepatic Impairment under **CLINICAL PHARMACOLOGY**, Special Populations) is limited.

SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see **Orthostatic Hypotension**).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases in dose.

Interference with Cognitive and Motor Performance: Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed if they are taking SEROQUEL.

Concomitant Medication: As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs.

Alcohol: Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Laboratory Tests
No specific laboratory tests are recommended.

Drug Interactions
The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL.

Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents.

SEROQUEL may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on Quetiapine
Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate) (see **DOSAGE AND ADMINISTRATION**).

Divalproex: Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine at steady state by 17% without affecting the extent of absorption or mean oral clearance.

Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg

tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A Inhibitors: Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin).

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine.

Effect of Quetiapine on Other Drugs

Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing.

Divalproex: The mean maximum concentration and extent of absorption of total and free valproic acid at steady state were decreased by 10 to 12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant.

Lithium: Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

Antipyrine: Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in **PRECAUTIONS, General**).

Mutagenesis: The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats.

Impairment of Fertility: Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C:

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of

50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of SEROQUEL on labor and delivery in humans is unknown.

Nursing Mothers: SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed.

Pediatric Use: The safety and effectiveness of SEROQUEL in pediatric patients have not been established.

Geriatric Use: Of the approximately 3400 patients in clinical studies with SEROQUEL, 7% (232) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly

compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients (see Pharmacokinetics under **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for SEROQUEL consisting of over 3000 patients. This database includes 405 patients exposed to SEROQUEL for the treatment of acute bipolar mania (monotherapy and adjunct therapy) and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL for the treatment of schizophrenia.

Of these approximately 3000 subjects, approximately 2700 (2300 in schizophrenia and 405 in acute bipolar mania) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 914.3 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Controlled Trials

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo- Controlled Trials

Bipolar Mania: Overall, discontinuations due to adverse events were 5.7 % for SEROQUEL vs. 5.1% for placebo in monotherapy and 3.6% for SEROQUEL vs. 5.9% for placebo in adjunct therapy.

Schizophrenia: Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **PRECAUTIONS**):

Adverse Event	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 800 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 1. Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials[1] for the Treatment of Schizophrenia and Bipolar Mania (monotherapy)

Body System/ Preferred Term	SEROQUEL (n=719)	PLACEBO (n=404)
Body as a Whole		
Headache	21%	14%
Pain	7%	5%
Asthenia	5%	3%
Abdominal Pain	4%	1%
Back Pain	3%	1%
Fever	2%	1%
Cardiovascular		
Tachycardia	6%	4%
Postural Hypotension	4%	1%

Digestive		
Dry Mouth	9%	3%
Constipation	8%	3%
Vomiting	6%	5%
Dyspepsia	5%	1%
Gastroenteritis	2%	0%
Gamma Glutamyl Transpeptidase Increased	1%	0%
Metabolic and Nutritional		
Weight Gain	5%	1%
SGPT Increased	5%	1%
SGOT Increased	3%	1%
Nervous		
Agitation	20%	17%
Somnolence	18%	8%
Dizziness	11%	5%
Anxiety	4%	3%
Respiratory		
Pharyngitis	4%	3%
Rhinitis	3%	1%
Skin and Appendages		
Rash	4%	2%
Special Senses		
Amblyopia	2%	1%

[1]Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypertonia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%).

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 3-weeks) of acute mania in 5% or more of patients treated with SEROQUEL (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 2. Treatment-Emergent Adverse Experience Incidence in 3-Week Placebo-Controlled Clinical Trials[1] for the Treatment of Bipolar Mania (Adjunct Therapy)

Body System/ Preferred Term	SEROQUEL (n=196)	PLACEBO (n=203)
Body as a Whole		
Headache	17%	13%
Asthenia	10%	4%
Abdominal Pain	7%	3%
Back Pain	5%	3%
Cardiovascular		
Postural Hypotension	7%	2%
Digestive		
Dry Mouth	19%	3%
Constipation	10%	5%
Metabolic and Nutritional		
Weight Gain	6%	3%
Nervous		
Somnolence	34%	9%
Dizziness	9%	6%
Tremor	8%	7%
Agitation	6%	4%
Respiratory		
Pharyngitis	6%	3%

[1]Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, and nausea.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%), postural hypotension (7%), pharyngitis (6%), and weight gain (6%).

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Dose-related Adverse Events: Spontaneously elicited adverse event data from a study of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain.

Extrapyramidal Symptoms: Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

	SEROQUEL					
Dose Groups	Placebo	75 mg	150 mg	300 mg	600 mg	750 mg
Parkinsonism	-0.6	-1.0	-1.2	-1.6	-1.8	-1.8
EPS incidence	16%	6%	6%	4%	8%	6%
Anticholinergic medications	14%	11%	10%	8%	12%	11%

In six additional placebo-controlled clinical trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS.

Vital Signs and Laboratory Studies

Vital Sign Changes: SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain: In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo.

Laboratory Changes: An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**).

An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between SEROQUEL and placebo.

ECG Changes: Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of

patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (1/192) for SEROQUEL compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria was 0.6% (1/166) for SEROQUEL compared to 0% (0/171) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**).

Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for schizophrenia. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Nervous System: ***Frequent:*** hypertonia, dysarthria; ***Infrequent:*** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; ***Rare:*** aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma.

Body as a Whole: ***Frequent:*** flu syndrome; ***Infrequent:*** neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; ***Rare:*** abdomen enlarged.

Digestive System: ***Frequent:*** anorexia; ***Infrequent:*** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; ***Rare:*** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis.

Cardiovascular System: ***Frequent:*** palpitation; ***Infrequent:*** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; ***Rare:*** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

Respiratory System: ***Frequent:*** pharyngitis, rhinitis, cough increased, dyspnea; ***Infrequent:*** pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation.

Metabolic and Nutritional System: ***Frequent:*** peripheral edema; ***Infrequent:*** weight loss, alkaline

phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** glycosuria, gout, hand edema, hypokalemia, water intoxication.

Skin and Appendages System: ***Frequent:*** sweating; ***Infrequent:*** pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; ***Rare:*** exfoliative dermatitis, psoriasis, skin discoloration.

Urogenital System: ***Infrequent:*** dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; ***Rare:*** gynecomastia*, nocturia, polyuria, acute kidney failure.

Special Senses: ***Infrequent:*** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: ***Infrequent:*** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

Hemic and Lymphatic System: ***Frequent:*** leukopenia; ***Infrequent:*** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia.

Endocrine System: ***Infrequent:*** hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism.

*adjusted for gender

Post Marketing Experience:
Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include: leukopenia/neutropenia. If a patient develops a low white

cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia.

Other adverse events reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, anaphylaxis, hyponatremia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Steven Johnson syndrome (SJS).

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: SEROQUEL is not a controlled substance.

Physical and Psychologic dependence: SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE

Human experience: Experience with SEROQUEL (quetiapine fumarate) in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been

very rare reports of overdose of SEROQUEL alone resulting in death, coma, or QTc prolongation.

Management of Overdosage:

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Bipolar Mania

Usual Dose: When used as monotherapy or adjunct therapy (with lithium or divalproex), SEROQUEL should be initiated in BID doses totaling 100 mg/day on Day 1, increased to 400 mg/day on Day 4 in increments of up to 100 mg/day in BID divided doses. Further dosage

adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day. Data indicates that the majority of patients responded between 400 to 800 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Schizophrenia

Usual Dose: SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state for SEROQUEL would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25-50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective.

Efficacy in schizophrenia was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions (see **CLINICAL PHARMACOLOGY**). When indicated, dose escalation should be performed with caution in these patients.

Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital (See Drug Interactions under **PRECAUTIONS**).

Maintenance Treatment: While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should remain on it, the effectiveness of maintenance treatment is well established for many other drugs used to treat schizophrenia. It is recommended that responding patients be continued on SEROQUEL, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off SEROQUEL, titration of SEROQUEL is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed.

Switching from Antipsychotics: There are no systematically collected data to specifically address switching patients with schizophrenia from antipsychotics to SEROQUEL, or concerning concomitant administration with antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate SEROQUEL therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '25' on one side and plain on the other side, are supplied in bottles of 100 tablets and 1000 tablets, and hospital unit dose packages of 100 tablets.

100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with 'SEROQUEL' and '100' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

200 mg Tablets (NDC 0310-0272) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '200' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

300 mg Tablets (NDC 0310-0274) white, capsule-shaped, biconvex, film coated tablets, intagliated with 'SEROQUEL' on one side and '300' on the other side, are supplied in bottles of 60 tablets, and hospital unit dose packages of 100 tablets.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP].

ANIMAL TOXICOLOGY

Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2 year carcinogenicity study. Doses were 10-250 mg/kg in rats, 75-750 mg/kg in mice; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.

AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
Made in USA

Rev. 06/05 SIC 30139-00

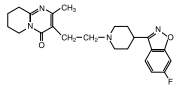
Clinical Study Protocol: Appendix G	
Drug substance:	quetiapine fumarate
Study Code:	5077IL/0089
Appendix Edition No:	1
Appendix Date:	

Appendix G
Risperdal Package Insert

RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro- 2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets are available in 0.5 mg, 1.0 mg, and 2.0 mg strengths and are light coral in color.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10^{-5} M) for cholinergic muscarinic or $ß_1$ and $ß_2$ adrenergic receptors.

Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPERDAL® M-TAB™ Orally Disintegrating Tablets are bioequivalent to RISPERDAL® Tablets.

Plasma concentrations of risperidone, its major metabolite, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9-hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady state in about 5 days in poor metabolizers. Steady-state concentrations of 9-hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 μg/mL), warfarin (10 μg/mL), and carbamazepine (10 μg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydrox-yrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through *N*-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug (i.e., the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

Risperidone could be subject to two kinds of drug-drug interactions (see Drug Interactions under PRECAUTIONS). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n≅70) of poor metabolizers given risperidone do not suggest important differences between poor and extensive metabolizers. Second, co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause a decrease in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of ^{14}C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and 20 hours (CV=40%) in poor metabolizers. The apparent half-life of 9-hydroxyrisperidone was about 21 hours (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacokinetics of the active moiety, after single and multiple doses, were similar in extensive and poor metabolizers, with an overall mean elimination half-life of about 20 hours.

Special Populations

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and its active metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should be reduced in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL® doses should be reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly

In healthy elderly subjects renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives were prolonged compared to young healthy subjects. Dosing should be modified accordingly in the elderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether corrected for body weight or not) or race.

Clinical Trials

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four short-term (4 to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophrenia.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, two more recently developed, but less well evaluated scales, were employed; these included the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS).

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6 to 8 weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® has not been shown to be safe or effective in the treatment of patients with dementia-related psychosis.

Potential for Proarrhythmic Effects

Risperidone and/or 9-hydroxyrisperidone appear to lengthen the QT interval in some patients, although there is

no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrhythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures

During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL®-treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia

As with other drugs that antagonize dopamine D$_2$ receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see CARCINOGENESIS). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism

Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness

Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and the data revealed one finding of potential concern, i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment; no such prolongations were seen in the smaller placebo group. There were 3 such episodes in the approximately 125 patients who received haloperidol. Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (see WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance

Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing

Patients should be advised not to breast-feed an infant if they are taking RISPERDAL®.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL®.

Phenylketonurics

Phenylalanine is a component of aspartame. Each 2 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.56 mg phenylalanine; each 1 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB™ Orally Disintegrating Tablet contains 0.14 mg phenylalanine.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Carbamazepine and Other Enzyme Inducers

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment.

Fluoxetine

Fluoxetine (20 mg QD) has been shown to increase the plasma concentration of risperidone 2.5-2.8 fold, while the plasma concentration of 9-hydroxyrisperidone was not affected. When concomitant fluoxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Lithium

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13).

Valproate

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone.

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n≅70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, MP, and 3A4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m^2 (mg/kg) basis at which these tumors occurred.

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m^2 (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6 (37.5)	1.5 (9.4)
Mammary gland neoplasms, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5 to 6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, *in vitro* rat hepatocyte DNA-repair assay, *in vivo* micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m^2 basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m^2 basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m^2 basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant

exposed to risperidone *in utero*. The causal relationship to RISPERDAL® therapy is unknown.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9-hydroxyrisperidone are excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast- feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated With Discontinuation of Treatment

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in Phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients compared to 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® compared to placebo patients, it is unlikely that suicide attempt is a RISPERDAL® related adverse event (see PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients, but 3.8% in active-control patients in the Phase 2-3 trials.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

In two 6 to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events occurred at an incidence of at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Patients

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL®-treated patients treated at doses of ≤ 10 mg/day than among placebo-treated patients in the pooled results of two 6 to 8-week controlled trials. Patients received RISPERDAL® doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg/day in the titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 16 mg/day) who spontaneously reported at least one episode of an event at some time during their treatment. Patients given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were classified using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Table 1 Incidence of Treatment-Emergent Adverse Events in 6 to 8-Week Controlled Clinical Trials[1]

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Central & peripheral nervous system			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory system			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a whole - general			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see DOSE DEPENDENCY OF ADVERSE EVENTS).

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 4 fixed doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean change from baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous complaints of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

Vital Sign Changes

RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes

The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6 to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes

A between-group comparison for 6 to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes

The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (see WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Premarketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (risperidone) were administered to 2607 patients in Phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included, except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders

Frequent: increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastrointestinal Disorders

Frequent: anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders

Frequent: fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders

Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders

Frequent: increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders

Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders

Infrequent: abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders

Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders

Frequent: polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-Skeletal System Disorders

Infrequent: myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female

Frequent: menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders

Infrequent: increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding, and Clotting Disorders

Infrequent: epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders

Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders

Infrequent: anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male

Frequent: erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders

Rare: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders

Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses

Rare: bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, hyperglycemia, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychologic Dependence

RISPERDAL® has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdosage with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure. Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, and hypotension. Other adverse events reported since market introduction which were temporally, (but not necessarily causally) related to RISPERDAL® overdose, include prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality associated with multiple drug overdose.

Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. Because of the rapid disintegration of risperidone orally disintegrating tablets, pill fragments may not appear in gastric contents obtained with lavage.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Usual Initial Dose

RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®; however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Pediatric Use

Safety and effectiveness of RISPERDAL® in pediatric patients have not been established.

Dosage in Special Populations

The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Directions for Use of RISPERDAL® M-TAB™ Orally Disintegrating Tablets

RISPERDAL® M-TAB™ Orally Disintegrating Tablets are supplied in blister packs of 4 tablet units each.

Tablet Accessing

Do not open the blister until ready to administer. For single tablet removal, separate one of the four blister units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to expose the tablet. DO NOT push the tablet through the foil because this could damage the tablet.

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place the entire RISPERDAL® M-TAB™ Orally Disintegrating Tablet on the tongue. The RISPERDAL® M-TAB™ Orally Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once removed from the blister unit. RISPERDAL® M-TAB™ Orally Disintegrating Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid. Patients should not attempt to split or to chew the tablet.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day, and to a target dose of 4 mg QD on the third day (see Clinical Trials, under CLINICAL PHARMACOLOGY). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0.25", "0.5", or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-50.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bottles of 500 NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bottles of 500 NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bottles of 500 NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bottles with a calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, while the maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

RISPERDAL® M-TAB™ (risperidone) Orally Disintegrating Tablets are etched on one side with R0.5, R1, and R2, respectively, and are packaged in blister packs of 4 (2 X 2) tablets.

0.5 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-395-28, bingo card of 30 tablets NDC 50458-395-30.

1 mg light coral, square, biconvex tablets: 7 blister packages per box, NDC 50458-315-28, bingo card of 30 tablets NDC 50458-315-30.

2 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-325-28.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.
Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (59°-77°F). Protect from light and freezing.
Keep out of reach of children.

RISPERDAL® M-TAB™ Orally Disintegrating Tablets should be stored at controlled room temperature 15°-25°C (59°-77°F).
Keep out of reach of children.

7519700
US Patent 4,804,663
Revised April 2003

RISPERDAL® tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico or
Janssen-Cilag, SpA, Latina, Italy

RISPERDAL® oral solution is manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium

RISPERDAL® M-TAB™ Orally Disintegrating Tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico

RISPERDAL® tablets, RISPERDAL® M-TAB™ Orally Disintegrating Tablets, and oral solution are distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

JANSSEN PHARMACEUTICA PRODUCTS, L.P.

Clinical Study Protocol: Appendix H	
Drug substance:	quetiapine fumarate
Study Code:	5077IL/0089
Appendix Edition No:	1
Appendix Date:	

Appendix H
Declaration of Helsinki

Recommendations guiding physicians in biomedical research involving human subjects.

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975 and the 35th World Medical Assembly, Venice, Italy, October 1983 and the 41st World Medical Assembly Hong Kong, September 1989 and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of The World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient´s interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject´s physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject´s freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor´s consent must be obtained in addition to the consent of the minor´s legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with professional care (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical re-search involving human subjects
(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient´s illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

AstraZeneca

Clinical Study Protocol: Appendix I	
Drug Substance	quetiapine fumarate
Study Code	5077IL/0089
Edition No.	1
Appendix Date	

Appendix I
Insurance and Indemnity

INSURANCE AND INDEMNITY

AstraZeneca's liability is covered by a liability insurance policy with AstraZeneca Insurance Company Limited, policy No.: L/702938.

With respect to any liability directly or indirectly caused by the investigational products in connection with this Clinical Study, AstraZeneca assumes liability by law on behalf of the investigator(s) and his assistants for possible injury to the subject provided the investigator(s) and his assistants have followed the instructions of AstraZeneca in accordance with this protocol and any amendments thereto, that the investigational products administered to the subject in this Clinical Study have been supplied by AstraZeneca and that the investigator and his assistants have in general performed this clinical study in accordance with scientific practice and currently acceptable techniques and know-how.

AstraZeneca can forward a letter of indemnity if needed by the investigator(s)/institution.

AstraZeneca

Clinical Study Protocol: Appendix J	
Drug Substance	quetiapine fumarate
Study Code	5077IL/0089
Edition No.	1
Appendix Date	

Appendix J
Investigators and Study Administrative Structure

STAFF AT INVESTIGATIONAL SITE(S)

Centre No.	**Centre address**	**Name** (First name, Last name)	**Qualifications**	**Present position**	**Role in the study**
<<>>					Principal investigator

ASTRAZENECA STUDY PERSONNEL

Address	**Name** (First name, Last name)	**Qualifications**	**Present Position**	**Role in the study**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DATA MONITORING OR SAFETY COMMITTEE(S)

Committee name and address	**Member name** (First name, Last name)	**Qualifications**	**Role in committee**
<<>>			

OTHER PARTICIPANTS

Organisation and address	**Name** (First name, Last name)	**Qualifications**	**Present position**	**Role in study**
<<>>				

AstraZeneca

Appendix K

Check on: [x] **Final Draft CSP** [ ] **CSP Administrative change** [ ] **CSP Amendment** [ ] **Working Protocol**

Project/Study identification:

Drug name: quetiapine fumarate (SEROQUEL ™) **Protocol No.:** 5077IL/0089 **Protocol draft version No.** 1

Protocol title: A multicenter, open-label, flexible-dose, parallel-group evaluation of the cataractogenic potential of quetiapine fumarate (SEROQUEL™) and risperidone (RISPERDAL™) in the long-term treatment of patients with schizophrenia or schizoaffective disorder

Protocol author: [redacted]

Date distributed [redacted]

Reviewers:

Return to: [redacted]

Date due: [redacted]

Name	Title		
[redacted]			