QUETIAPINE 25MG, 100MG, 150MG, 200MG AND 300MG
FILM-COATED TABLETS

PL 24668/0163-7

UKPAR

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QUETIAPINE 25MG, 100MG, 150MG, 200MG AND 300MG FILM-COATED TABLETS

LAY SUMMARY

On 25th February 2011, the MHRA granted Caduceus Pharma Limited Marketing Authorisations (licences) for Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets.

Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets contain the active ingredient, quetiapine fumarate. Quetiapine fumarate belongs to a class of medicines called antipsychotics.

Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets are used to help with the effects of some types of mental illness such as:

- Hallucinations (like hearing unexplained voices), strange and frightening thoughts, changes in behaviour, and feeling alone and confused. This is also known as schizophrenia.
- Effects on mood and feeling very ‘high’ or excited. Symptoms of this can be needing to sleep less than usual, feeling more irritable than usual, or being more talkative and have racing thoughts or ideas. This is also known as bipolar mania.
- Effects on mood whereby you feel sad all the time. Symptoms of this can be feeling depressed, feeling guilty, lacking energy, loss of appetite and/or being unable to sleep. This is also known as bipolar depression.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
QUETIAPINE 25MG, 100MG, 150MG, 200MG AND 300MG
FILM-COATED TABLETS

PL 24668/0163-7

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted Caduceus Pharma Limited Marketing Authorisations for the medicinal products Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets (PL 24668/0163-7) on 25th February 2011. Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets are prescription only medicines (POM) and are indicated for the treatment of:

- Schizophrenia.
- Bipolar disorder including:
  - manic episodes associated with bipolar disorder
  - major depressive episodes in bipolar disorder
  - preventing recurrence in bipolar disorder in patients whose manic, mixed or depressive episode has responded to quetiapine treatment.

These applications for Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets are submitted under Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Seroquel 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets, first authorised in the UK to Zeneca Limited on 31st July 1997 and 19th April 1999 respectively (PL 12619/0112-4 and 0124). The licences for the reference products underwent a change of ownership to AstraZeneca UK Limited on 31st October 1997 and 25th June 2000 (PL 17901/0038-41 and 0088).

Quetiapine is a psychotropic agent belonging to a chemical class; the dibenzothiazepine is an antipsychotic agent, which combines potent serotonin (5-hydroxytryptamine) 5-HT2 and dopamine D2 receptor antagonism. The pharmacokinetics of quetiapine is well understood, having been studied in healthy young & elderly subjects as well as in psychotic patients.

The pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring.

A Risk Management Plan (RMP) has been set for the reference products, Seroquel 25mg, 100mg, 150mg, 200mg and 300mg tablets, with some provisions that also need to be applied for generic products. A formal RMP is not considered necessary, however, the Marketing Authorisation holder has provided a post-approval commitment to comply with risk minimisation measures now requested for quetiapine.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

INN: Quetiapine fumarate

Chemical name:
- 2-[2-(4-Dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol hemifumarate (2:1)
- 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)dibenzo[b,f][1,4]thiazepine hemifumarate

Structure:

Physical form: White or slightly yellow powder
Solubility: Sparingly soluble in glacial acetic acid (26.6 mg/ml) and slightly soluble in methanol (6.3 mg/ml), acetone (1.5 mg/ml) and water (1.5 mg/ml).

Molecular formula: \((C_{21}H_{25}N_{3}O_{2}S)_{2}C_{4}H_{4}O_{4}\)
Molecular weight: 883.09 (Quetiapine fumarate) 383.51 (Quetiapine base)

Quetiapine fumarate is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof of structure data has been supplied for the active pharmaceutical ingredients. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all reference standards used.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.
DRUG PRODUCT

Other ingredients

Other ingredients in the tablet core consist of pharmaceutical excipients microcrystalline cellulose, povidone K29-32, calcium hydrogen phosphate dihydrate, sodium starch glycolate (Type A), lactose monohydrate and magnesium stearate.

Ingredients in the film-coating are:
25mg: Opadry II Pink 33G34594 containing: hypromellose 6cP, titanium dioxide, lactose monohydrate, macrogol 3350, triacetin, iron oxide yellow (E172) and iron oxide red (E172).

100mg: Opadry II Yellow 33G32578 containing: hypromellose 6cP, titanium dioxide, lactose monohydrate, macrogol 3350, triacetin and iron oxide yellow (E172).

150mg: Opadry II Yellow 33G32605 containing: hypromellose 6cP, titanium dioxide, lactose monohydrate, macrogol 3350, triacetin and iron oxide yellow (E172).

200mg: Opadry II White 33G28435 containing: hypromellose 6cP, titanium dioxide, lactose monohydrate, macrogol 3350 and triacetin

300mg: Opadry II White 33G28435 containing: hypromellose 6cP, titanium dioxide, lactose monohydrate, macrogol 3350 and triacetin.

All the ingredients with the exception of iron oxide yellow (E172) and iron oxide red (E172) comply with their relevant European Pharmacopoeia monographs. Iron oxide yellow (E172) and iron oxide red (E172) comply with in-house specifications.

None of the excipients used contain material of human origin. The supplier has confirmed that the magnesium stearate contained in this product is sourced from vegetable origin.

The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption and it is prepared without the use of any other ruminant materials, with the exception of calf rennet, the production of which complies with EU legislation.

Product development

The objective of the development programme was to produce quetiapine fumarate containing products that could be considered generic medicinal products of Seroquel 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets (Zeneca Limited).

The reference product used in the bioequivalence study is Seroquel 25mg Film-coated Tablets, authorised in Germany to AstraZeneca GmbH. The German product is considered qualitatively and quantitatively similar to the UK reference product.

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative in vitro impurity and dissolution profiles have been provided for the proposed and originator products.
**Manufacture**
A description and flow-chart of the manufacturing method has been provided. Satisfactory batch formulae have been provided for the manufacture of the products. The manufacturing process has been validated and has shown satisfactory results. In-process controls are satisfactory based on batch data and controls on the finished products. Process validation data on pilot-scale batches of each strength have been provided and are satisfactory. The applicant has committed to perform process validation on commercial-scale batches of each strength.

**Finished product specification**
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis for all working standards used have been provided and are satisfactory.

**Container-Closure System**
The tablets are packaged in:
i) Blisters composed of:
   - polyvinyl chloride (PVC), polyvinylidene chloride (PVDC) and aluminium
   - PVC and aluminium

ii) Polyethylene tablet containers.

Pack sizes are 6, 10, 20, 30, 50, 60, 90, 100 tablets.

Specifications and Certificates of Analysis have been provided. All primary product packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf life of 36 months has been set, with no special storage instructions. This is satisfactory.

**ADMINISTRATIVE**

**Expert Report**
A quality overall summary has been written by a suitably qualified person and is satisfactory.

**Summary of Product Characteristics (SmPCs)**
These are pharmaceutically satisfactory.

**Labelling**
These are pharmaceutically satisfactory.

**Patient Information Leaflet (PILs)**
This is pharmaceutically satisfactory.

**MAA Forms**
These are pharmaceutically satisfactory.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with these applications and none are required for applications of this type.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support the applications, the Marketing Authorisation Holder has included a single bioequivalence study:

A randomised, open-label, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study comparing the pharmacokinetics of Quetiapine 25mg Film-coated Tablets (Test) versus Seroquel® 25mg Film-coated Tablets (Reference) in healthy volunteers under fasting conditions.

Blood sampling was performed pre-dose and up to 36 hours post dose in each treatment period. There was a washout period of 7 days. Plasma levels of quetiapine were determined by a validated LC-MS / MS method. Pharmacokinetic parameters were calculated and statistically analysed.

Results from this study are presented below as log-transformed values:

Geometric Least Mean Squares and 90% Confidence Interval

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters of quetiapine fumarate</th>
<th>AUC_{0-t} (pg.h/mL)</th>
<th>AUC_{0-∞} (pg.h/mL)</th>
<th>C_{max} (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
<td>505.480</td>
<td>519.742</td>
<td>110.405</td>
</tr>
<tr>
<td><strong>Reference</strong></td>
<td>472.848</td>
<td>487.916</td>
<td>101.412</td>
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<tr>
<td><strong>Ratio (90% CI)</strong></td>
<td>1.08</td>
<td>1.08</td>
<td>1.09</td>
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<td>(1.01 – 1.16)</td>
<td>(1.01 – 1.16)</td>
<td>(0.99 – 1.20)</td>
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The applicant adequately justified the use of the 25mg product for the bioequivalence study rather than the usual higher dose (300mg). The lowest dose of 25mg was selected because of safety concerns if healthy subjects were used for 100mg (or higher strength) testing. Considering that the pharmacokinetics of quetiapine are linear over the therapeutic range, this is satisfactory.

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for quetiapine lie within the normal 80-125% limits. Thus, bioequivalence has been shown between the test and reference products.

As the 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablet strengths meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 25mg strength can be extrapolated to Quetiapine 100mg, 150mg, 200mg and 300mg Film-coated Tablets.

EFFICACY
These are generic applications based on demonstration of bioequivalence and new data relating to efficacy are not required as per EU legislation once bioequivalence has been demonstrated.
SAFETY
These are generic applications based on demonstration of bioequivalence and new data relating to safety are not required as per EU legislation once bioequivalence has been demonstrated.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORMS (MAA)
These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPCs)
These are consistent with those for the reference products and are satisfactory.

DISCUSSION
The applicant has satisfactorily demonstrated bioequivalence between the test and reference products.

MEDICAL CONCLUSION
The bioequivalence study submitted, together with the additional data provided has shown that Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets can be considered as generic medicinal products to the reference products Seroquel 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets.

The grant of Marketing Authorisations is recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Quetiapine 25mg Film-coated Tablets and the reference product. This conclusion can be extrapolated to Quetiapine 100mg, 150mg, 200mg and 300mg Film-coated Tablets.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with quetiapine fumarate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
**QUETIAPINE 25MG, 100MG, 150MG, 200MG AND 300MG FILM-COATED TABLETS**

**STEPS TAKEN FOR ASSESSMENT**

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<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation Applications on 26(^{th}) January 2009.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 6(^{th}) February 2009.</td>
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| 3 | Following assessment of the application, the MHRA requested further information relating to the quality dossier on 23\(^{rd}\) April 2009 and 26\(^{th}\) November 2011.  
Further information relating to the clinical dossier was requested on 26\(^{th}\) November 2009. |
| 4 | The applicant responded to the MHRA’s requests, providing further information on 17\(^{th}\) October 2009 and 29\(^{th}\) June 2010 for the quality section.  
Further information for the clinical section was provided on 29\(^{th}\) June 2010. |
| 5 | The applications were determined on 25\(^{th}\) February 2011. |
QUETIAPINE 25MG, 100MG, 150MG, 200MG AND 300MG FILM-COATED TABLETS

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Quetiapine 25mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 25mg quetiapine (as fumarate).

Excipients:
Each tablet contains 5.175 mg lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Light orange, 5.5 mm, round, biconvex, engraved with Q on one side

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Quetiapine is indicated for the treatment of:
Schizophrenia.

Bipolar disorder including:
- manic episodes associated with bipolar disorder
- major depressive episodes in bipolar disorder
- preventing recurrence in bipolar disorder in patients whose manic, mixed or depressive episode has responded to quetiapine treatment.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Quetiapine Film-coated Tablets can be administered with or without food.

Adults
For the treatment of schizophrenia: Quetiapine should be administered twice a day. The total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4).

From Day 4 onwards, the dose should be titrated to the usual effective dose range of 300 to 450 mg/day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 to 750 mg/day.

For the treatment of manic episodes associated with bipolar disorder: Quetiapine should be administered twice a day. As monotherapy or as adjunct to mood stabilisers, the total daily dose for the first four days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg per day by Day 6 should be in increments of no greater than 200 mg per day.

The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg per day. The usual effective dose is in the range of 400 to 800 mg per day.

For the treatment of depressive episodes in bipolar disorder: Quetiapine should be administered once daily at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group. Individual patients may benefit from a 600 mg dose. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered. When treating depressive episodes in bipolar disorder, treatment should be initiated by physicians experienced in treating bipolar disorder.

For preventing recurrence in bipolar disorder: For prevention of recurrence of manic, depressive and mixed episodes in bipolar disorder, patients who have responded to quetiapine for acute treatment of bipolar disorder should continue therapy at the same dose. The dose may then be adjusted depending on clinical response and tolerability of the individual patient, within the range of
300 to 800 mg/day administered twice daily. It is important that the lowest effective dose is used for maintenance therapy.

**Elderly**

As with other antipsychotics, Quetiapine Film-coated Tablets should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on Quetiapine Film-coated tablets 25 mg/day. The dose should be increased daily in increments of 25 to 50 mg, to an effective dose, which is likely to be lower than that in younger patients.

Efficacy and safety have not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

**Children and adolescents**

Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in sections 4.4, 4.8, 5.1 and 5.2.

**Renal impairment**

Dose adjustment is not necessary in patients with renal impairment.

**Hepatic impairment**

Quetiapine is extensively metabolised by the liver. Therefore, quetiapine should be used with caution in patients with known hepatic impairment, especially during the initial dose titration period. Patients with known hepatic impairment should be started with 25 mg/day. The dosage should be increased daily with increments of 25 - 50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.

### 4.3 CONTRAINDICATIONS

Quetiapine film-coated tablets are contraindicated in patients who are hypersensitive to any component of this product.

Concomitant administration of cytochrome P450 3A4 inhibitors such as HIV protease inhibitors,azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated. (See also section 4.5 Interaction with other medicinal products and other forms of interaction).

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Children and adolescents (10 to 17 years of age)**

Quetiapine Film-coated tablets are not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials have shown that in addition to the known safety profile identified in adults (see section 4.8 Undesirable effects), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, and extrapyramidal symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

Furthermore, the long-term safety implications of treatment on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

In placebo-controlled clinical trials with children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia and bipolar mania (see section 4.8 Undesirable effects).

**Suicide/suicidal thoughts or clinical worsening**

Depression in bipolar disorder is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
In clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients less than 25 years of age who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively).

**Somnolence**
Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see Section 4.8 Undesirable effects). In clinical trials for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

**Cardiovascular disease**
Quetiapine Film-coated Tablets should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.

Quetiapine may induce orthostatic hypotension, especially during the initial dose-titration period; this is more common in elderly patients than in younger patients. Dose reduction or more gradual titration should be considered if this occurs.

**Seizures**
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with Quetiapine or placebo. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see section 4.8 Undesirable effects).

**Extrapyramidal symptoms**
In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder (see Section 4.8 Undesirable effects).

**Tardive dyskinesia**
Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic drugs including quetiapine. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Quetiapine Film-coated Tablets should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see section 4.8 Undesirable effects).

**Neuroleptic malignant syndrome**
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including Quetiapine Film-coated Tablets (see Section 4.8 Undesirable effects). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, Quetiapine Film-coated Tablets should be discontinued and appropriate medical treatment given.

**Severe neutropenia**
Severe neutropenia (neutrophil count < 0.5 X 10^9/L) has been uncommonly reported in quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with Quetiapine. There was no apparent dose relationship. During post-marketing experience, resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count < 1.0 X 10^7/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X 10^7/L). (See section 5.1 Pharmacodynamic properties).

**Interactions**
See also Section 4.5 Interactions with other medicinal products and other forms of interaction.

Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of quetiapine
treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer treatment is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

Hyperglycaemia
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported during treatment with quetiapine. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

Lipids
Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8 Undesirable effects). Lipid changes should be managed as clinically appropriate.

QT prolongation
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT interval. However, with overdose (see section 4.9) QT prolongation was observed. As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when quetiapine is prescribed with medicines known to increase QTc interval, and concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Acute withdrawal reactions
Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability have been described after abrupt cessation of quetiapine. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Gradual withdrawal over a period of at least one to two weeks is advisable (see Section 4.8 Undesirable effects).

Elderly patients with dementia-related psychosis
Quetiapine is not approved for the treatment of patients with dementia-related psychosis.

An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomized placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with an increased risk of stroke.

In a meta-analysis of atypical antipsychotic drugs, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. However in two 10-week placebo-controlled quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% compared to 3.2% in the placebo group. The patients in these trials died of a variety of causes that were consistent with expectations for this population. These data do not show causal relationship between quetiapine treatment and death in elderly patients with dementia.

Hepatic effects
If jaundice develops, Quetiapine film-coated tablets should be discontinued.

Concomitant illness
Dysphagia (see Section 4.8 Undesirable effects) and aspiration have been reported with Quetiapine. Although a causal relationship with aspiration pneumonia has not been established, Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures undertaken.
Lactose
Quetiapine Film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Additional information
Quetiapine data in combination with divalproex (valproate semisodium) or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 Undesirable effects and 5.1 Pharmacodynamic properties). The data showed an additive effect at week 3.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Given the primary central nervous system effects of quetiapine, it should be used with caution in combination with other centrally acting drugs and alcohol.

Cytochrome P450 (CYP) 3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine and a CYP3A4 inhibitor is contraindicated. It is also not recommended to take quetiapine together with grapefruit juice.

Quetiapine did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. However, in a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur which can influence the effect of quetiapine therapy. Co-administration of quetiapine and phenytoin (microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approximately 450%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine therapy should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer treatment is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate) (see also section 4.4 Special warnings and special precautions for use).

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 inhibitor).

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However co-administration of quetiapine and thioridazine caused increases in the clearance of quetiapine of about 70%.

The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine, a known P450 enzyme inhibitor.

The pharmacokinetics of lithium were not altered when co-administered with quetiapine.

The pharmacokinetics of valproic acid and quetiapine were not altered to a clinically relevant extent when co-administered as valproate semisodium (also known as divalproex sodium (USAN)) and Quetiapine film-coated tablets (quetiapine fumarate). Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.

Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QTc interval.

4.6 PREGNANCY AND LACTATION
The safety and efficacy of quetiapine during human pregnancy have not yet been established. Up to now there are no indications for harmfulness in animal tests, possible effects on the foetal eye have
not been examined though. Therefore, Quetiapine should only be used during pregnancy if the benefits justify the potential risks. Following pregnancies in which Quetiapine was used, neonatal withdrawal symptoms were observed.

The degree to which quetiapine is excreted into human milk is unknown. Women who are breast feeding should therefore be advised to avoid breast feeding while taking Quetiapine Film-coated Tablets.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness and may cause somnolence. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility to this is known.

4.8 UNDESIRABLE EFFECTS

The most commonly reported Adverse Drug Reactions (ADRs) with Quetiapine Film-coated Tablets are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension, and dyspepsia.

As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with Quetiapine Film-coated Tablets.

The incidences of ADRs associated with quetiapine therapy, are tabulated below according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

**Blood and lymphatic system disorders**
- **Common:** Leucopenia
- **Uncommon:** Eosinophilia, Thrombocytopenia
- **Unknown:** Neutropenia

**Immune system disorders**
- **Uncommon:** Hypersensitivity
- **Very rare:** Anaphylactic reaction

**Endocrine disorders**
- **Common:** Hyperprolactinaemia

**Metabolism and nutritional disorders**
- **Common:** Increased appetite
- **Very rare:** Diabetes Mellitus

**Psychiatric disorders**
- **Common:** Abnormal dreams and nightmares

**Nervous system disorders**
- **Very Common:** Dizziness, somnolence, headache
- **Common:** Syncope, Extrapyramidal symptoms, Dysarthria
- **Uncommon:** Seizure, Restless leg syndrome,
Tardive dyskinesia ¹

**Cardiac disorders**

*Common:* Tachycardia ⁴

**Eye disorders**

*Common:* Vision blurred

**Vascular disorders**

*Common:* Orthostatic hypotension ⁴, ¹⁷

**Respiratory, thoracic and mediastinal disorders**

*Common:* Rhinitis

**Gastrointestinal disorders**

*Very Common:* Dry mouth

*Common:* Constipation, dyspepsia

*Uncommon:* Dysphagia ⁸

**Hepato-biliary disorders**

*Rare:* Jaundice ⁶

*Very rare:* Hepatitis ⁶

**Skin and subcutaneous tissue disorders**

*Very rare:* Angioedema ⁶, Stevens-Johnson syndrome ⁶

**Reproductive system and breast disorders**

*Rare:* Priapism, galactorrhoea

**General disorders and administration site conditions**

*Very Common:* Withdrawal (discontinuation) symptoms ¹, ¹⁰

*Common:* Mild asthenia, peripheral oedema, irritability

*Rare:* Neuroleptic malignant syndrome ¹

**Investigations**

*Very Common:* Elevations in serum triglyceride levels ¹¹, elevations in total cholesterol (predominantly LDL cholesterol) ¹², decreases in HDL cholesterol ¹⁸, weight gain ⁹

*Common:* Elevations in serum transaminases (ALT, AST) ³, decreased neutrophil count, blood glucose increased to hyperglycaemic levels ⁷

*Uncommon:* Elevations in gamma-GT levels ³, platelet count decreased ¹⁴

*Rare:* Elevations in blood creatine phosphokinase ¹⁵, Venous thromboembolism ¹

(1) See section 4.4 Special Warnings and Special Precautions for Use.

(2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of SEROQUEL.
(3) Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT levels have been observed in some patients administered SEROQUEL.

(4) As with other antipsychotics with alpha, adrenergic blocking activity, SEROQUEL may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. (See section 4.4 Special warnings and special precautions for use).

(5) Exacerbation of pre-existing diabetes has been reported in very rare cases.

(6) Calculation of frequency for these ADRs have been taken from post-marketing data only.

(7) Fasting blood glucose ≥ 7.0 mmol/L or a non fasting blood glucose ≥ 11.1 mmol/L on at least one occasion.

(8) An increase in the rate of dysphagia with SEROQUEL vs. placebo was only observed in the clinical trials in bipolar depression.

(9) Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.

(10) The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.

(11) Triglycerides ≥ 200 mg/dL (≥ 2.258 mmol/L) (patients ≥ 18 years of age) or ≥ 150 mg/dL (≥ 1.694 mmol/L) (patients < 18 years of age) on at least one occasion.

(12) Cholesterol ≥ 240 mg/dL (≥ 6.2064 mmol/L) (patients ≥ 18 years of age) or ≥ 200 mg/dL (≥ 5.172 mmol/L) (patients < 18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥ 30 mg/dL (≥ 0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥ 1.07 mmol/L).

(13) See text below.

(14) Platelets < 100 x 10^9/L on at least one occasion.

(15) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.

(16) Prolactin levels (patients >18 years of age): >20 μg/L (>869.56 pmol/L) males; >30 μg/L (>1304.34 pmol/L) females at any time.

(17) May lead to falls.

(18) HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported with the use of neuroleptics and are considered class effects (see Section 4.4 Special warnings and special precautions for use).

In short-term, placebo-controlled clinical trials in bipolar depression the aggregated incidence of extrapyramidal symptoms was 8.9% for Quetiapine compared to 3.8% for placebo, though the incidence of the individual adverse events were generally low and did not exceed 4% in any treatment group. In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for Quetiapine and 8.0% for placebo; bipolar mania: 11.2% for Quetiapine and 11.4% for placebo).
Quetiapine treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T₄ and free T₄. The reduction in total and free T₄ was maximal within the first two to four weeks of quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T₄, irrespective of the duration of treatment. Smaller decreases in total T₃ and reverse T₃ were seen only at higher doses. Levels of Thyroxine-binding Globulin (TBG) were unchanged and in general, reciprocal increases in Thyroid stimulating hormone (TSH) were not observed, with no indication that quetiapine causes clinically relevant hypothyroidism.

4.9 OVERDOSE

Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of quetiapine alone. However, survival has also been reported following acute overdoses of up to 30 grams.

In post-marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma or QT-prolongation.

In general, reported signs and symptoms were those resulting from an exaggeration of the known pharmacological effects of the active substance, i.e. drowsiness and sedation, tachycardia and hypotension.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See section 4.4 : Special warnings and special precautions for use: Cardiovascular).

Management

There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal should be considered.

Close medical supervision and monitoring should be continued until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic Group: Antipsychotics
Therapeutic classification: N05AH04

Mechanism of action

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit an affinity for brain serotonin (5HT₂) and dopamine D₁ and D₂ receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT₂ relative to D₂ receptors which is believed to contribute to the antipsychotic properties and low extrapyramidal symptoms (EPS) liability of quetiapine compared to typical antipsychotics. Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic α₁ receptors, with a lower affinity for adrenergic α₂-receptors and serotonin 5HT₁A receptors.

Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

Pharmacodynamic effect

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D₂-receptor blockade. In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D₂ receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D₂ receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones.
following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration. The extent to which the norquetiapine metabolite contributes to the pharmacological activity of Quetiapine in humans is not known.

**Clinical Efficacy**

The results of three placebo-controlled clinical trials in patients with schizophrenia, including one that used a dose range of Quetiapine of 75 to 750 mg/day, identified no difference between Quetiapine and placebo in the incidence of EPS or use of concomitant anticholinergics. In four controlled trials, evaluating doses of Quetiapine up to 800 mg for the treatment of bipolar mania, two each in monotherapy and as adjunct therapy to lithium or valproate semisodium, there were no differences between the Quetiapine and placebo treatment groups in the incidence of EPS or concomitant use of anticholinergics.

In clinical trials, Quetiapine has been shown to be effective in the treatment of both positive and negative symptoms of schizophrenia. In one trial against chlorpromazine, and two against haloperidol, Quetiapine showed similar short-term efficacy.

In clinical trials, Quetiapine has been shown to be effective as monotherapy or as adjunct therapy in reducing manic symptoms in patients with bipolar mania. The mean last week median dose of Quetiapine in responders, was approximately 600 mg and approximately 85% of the responders were in the dose range of 400 to 800 mg per day.

In 4 clinical trials in patients with depressive episodes in bipolar I or bipolar II disorder, with and without rapid cycling courses, 51% of quetiapine treated patients had at least a 50% improvement in MADRS total score at week 8 compared to 37% of the placebo treated patients. The anti-depressant effect was significant at Day 8 (week 1). There were fewer episodes of treatment-emergent mania with Quetiapine than with placebo. In continuation treatment the anti-depressant effect was maintained for patients on Quetiapine (mean duration of treatment 30 weeks). Quetiapine reduced the risk of a recurrent mood (manic and depressed) event by 49%. Quetiapine was superior to placebo in treating the anxiety symptoms associated with bipolar depression as assessed by mean change from baseline to week 8 in HAM-A total score.

In one long-term study (up to 2 years treatment, mean quetiapine exposure 191 days) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed), in patients with bipolar I disorder. The number of patients with a mood event was 91 (22.5%) in the quetiapine group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups respectively. In patients who responded to quetiapine, when comparing continued treatment with quetiapine to switching to lithium, the results indicated that a switch to lithium treatment does not appear to be associated with an increased time to recurrence of a mood event. In two recurrence prevention studies evaluating Quetiapine in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with Quetiapine was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). The risk of a recurrent event was reduced by 70%. Quetiapine was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In placebo-controlled monotherapy trials in patients with a baseline neutrophil count $\geq 1.5 \times 10^9/L$, the incidence of at least one occurrence of neutrophil count $<1.5 \times 10^9/L$, was 1.72% in patients treated with Quetiapine compared to 0.73% in placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator; patients with a baseline neutrophil count $\geq 1.5 \times 10^9/L$), the incidence of at least one occurrence of neutrophil count $<0.5 \times 10^9/L$ was 0.21% in patients treated with Quetiapine and 0% in placebo treated patients and the incidence $\geq 0.5 - <1.0 \times 10^9/L$ was 0.75% in patients treated with Quetiapine and 0.11% in placebo-treated patients.

**Children and adolescents (10 to 17 years of age)**

The efficacy and safety of Quetiapine was studied in a 3-week placebo controlled study for the treatment of mania (n= 284 patients from the US, aged 10-17). About 45% of the patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo controlled study for the treatment of schizophrenia (n = 222 patients, aged 13-17) was performed. In both studies, patients with known lack of response to Quetiapine were excluded. Treatment with Quetiapine was initiated
at 50 mg/day and on day 2 increased to 100 mg/day; subsequently the dose was titrated to a target
dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day) using increments of 100 mg/day
given two or three times daily.

In the mania study, the difference in LS mean change from baseline in YMRS total score (active
minus placebo) was –5.21 for Quetiapine 400 mg/day and –6.56 for Quetiapine 600 mg/day.
Responder rates (YMRS improvement ≥ 50%) were 64% for Quetiapine 400 mg/day, 58% for 600
mg/day and 37% in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score
(active minus placebo) was –8.16 for Quetiapine 400 mg/day and –9.29 for Quetiapine 800 mg/day.
Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine was superior to
placebo with respect to the percentage of patients achieving response, defined as ≥ 30% reduction
from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in
numerically lower response rates.

No data are available on maintenance of effect or recurrence prevention in this age group.
A 26-week open-label extension to the acute trials (n= 380 patients), with Quetiapine flexibly dosed
at 400-800 mg/day, provided additional safety data. Increases in blood pressure were reported in
children and adolescents and increased appetite, extrapyramidal symptoms and elevations in serum
prolactin were reported with higher frequency in children and adolescents than in adult patients (see
Section 4.4 Special warnings and special precautions for use and Section 4.8 Undesirable effects).

Extrapyramidal Symptoms
In a short-term placebo-controlled monotherapy trial in adolescent patients (13-17 years of age) with
schizophrenia, the aggregated incidence of extrapyramidal symptoms was 12.9% for quetiapine and
5.3% for placebo, though the incidence of the individual adverse events (e.g. akathisia, tremor,
extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity,
dyskinesia) did not exceed 4.1% in any treatment group. In a short-term placebo-controlled
monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar mania, the
aggregated incidence of extrapyramidal symptoms was 3.6% for quetiapine and 1.1% for placebo. In
a long-term open label study of schizophrenia and bipolar mania, the aggregated incidence of
treatment-emergent EPS was 10%.

Weight Gain
In short-term clinical trials in paediatric patients (10-17 years of age), 17% of quetiapine-treated
patients and 2.5% of placebo-treated patients gained ≥ 7% of their body weight. When adjusting for
normal growth over longer term, an increase of at least 0.5 standard deviation from baseline in Body
Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who
were treated with quetiapine for at least 26 weeks met this criterion.

Suicide/Suicidal thoughts or Clinical worsening
In short-term placebo-controlled clinical trials in paediatric patients with schizophrenia, the
incidence of suicide related events was 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in
patients <18 years of age. In short-term placebo-controlled trials in paediatric patients with bipolar
mania, the incidence of suicide related events was 1.0% (2/193) for quetiapine and 0% (0/90) for
placebo in patients <18 years of age.

5.2 PHARMACOKINETIC PROPERTIES
Quetiapine is well absorbed and extensively metabolised following oral administration. The
bioavailability of quetiapine is not significantly affected by administration with food. Quetiapine is
approximately 83% bound to plasma proteins. Steady-state peak molar concentrations of the active
metabolite norquetiapine are 35% of that observed for quetiapine. The elimination half-lives of
quetiapine and norquetiapine are approximately 7 and 12 hours, respectively.

Clinical trials have demonstrated that Quetiapine is effective when given twice a day. This is further
supported by data from a positron emission tomography (PET) study which identified that 5HT2 and
D2 receptor occupancy are maintained for up to 12 hours after dosing with quetiapine.
The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range.
The kinetics of quetiapine do not differ between men and women.
The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in
adults aged 18 to 65 years.
The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73m²), but the individual clearance values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Quetiapine is extensively metabolised, with parent compound accounting for less than 5% of unchanged drug – related material in the urine or faeces, following the administration of radiolabelled quetiapine. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces. The mean quetiapine plasma clearance decreases by approx. 25% in persons with known hepatic impairment (stable alcoholcirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see section 4.2 Posology and method of administration).

In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

In a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of quetiapine given before and during treatment with ketoconazole, co–administration of ketoconazole resulted in an increase in mean Cmax and AUC of quetiapine of 235% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%. The mean half–life of quetiapine increased from 2.6 to 6.8 hours, but the mean tmax was unchanged.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Children and adolescents (10 to 17 years of age)
Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though Cmax in children was at the higher end of the range observed in adults. The AUC and Cmax for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

5.3 PRECLINICAL SAFETY DATA
There was no evidence of genotoxicity in a series of in vitro and in vivo genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in long-term clinical research:

In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy, a lowering in plasma T3 levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts.

Taking these findings into consideration, the benefits of the treatment with quetiapine need to be balanced against the safety risks for the patient.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Core
Microcrystalline cellulose
Povidone K29-32
Calcium hydrogen phosphate dihydrate
Sodium starch glycolate (Type A)
Lactose monohydrate
Magnesium stearate

**Film-coat**
Opadry II Pink 33G34594 containing:
Hypromellose 6cP
Titanium dioxide
Lactose monohydrate
Macrogol 3350
Triacetin
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 **INCOMPATIBILITIES**
Not applicable

6.3 **SHELF LIFE**
36 months

6.4 **SPECIAL PRECAUTIONS FOR STORAGE**
This medicinal product does not require any special storage conditions

6.5 **NATURE AND CONTENTS OF CONTAINER**
Blisters (PVC/PVDC/Al and PVC/Al) Pack sizes: 6, 10, 20, 30, 50, 60, 90, 100 tablets*
Plastic (polyethylene) tablet containers Pack sizes: 6, 10, 20, 30, 50, 60, 90, 100 tablets*
*Not all pack sizes may be marketed

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**
No special requirements

7 **MARKETING AUTHORISATION HOLDER**
Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 24668/0163

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
25/02/2011

10 **DATE OF REVISION OF THE TEXT**
25/02/2011
1 NAME OF THE MEDICINAL PRODUCT
Quetiapine 100mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100mg quetiapine (as fumarate).

Excipients:
Each tablet contains 20.7 mg lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Yellow, 8.5 mm, round, biconvex, engraved with Q on one side

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Quetiapine is indicated for the treatment of:
Schizophrenia.

Bipolar disorder including:
- manic episodes associated with bipolar disorder
- major depressive episodes in bipolar disorder
- preventing recurrence in bipolar disorder in patients whose manic, mixed or depressive episode has responded to quetiapine treatment.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Quetiapine Film-coated Tablets can be administered with or without food.

Adults
For the treatment of schizophrenia: Quetiapine should be administered twice a day. The total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4).

From Day 4 onwards, the dose should be titrated to the usual effective dose range of 300 to 450 mg/day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 to 750 mg/day.

For the treatment of manic episodes associated with bipolar disorder: Quetiapine should be administered twice a day. As monotherapy or as adjunct to mood stabilisers, the total daily dose for the first four days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg per day by Day 6 should be in increments of no greater than 200 mg per day.

The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg per day. The usual effective dose is in the range of 400 to 800 mg per day.

For the treatment of depressive episodes in bipolar disorder: Quetiapine should be administered once daily at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group. Individual patients may benefit from a 600 mg dose. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered. When treating depressive episodes in bipolar disorder, treatment should be initiated by physicians experienced in treating bipolar disorder.

For preventing recurrence in bipolar disorder: For prevention of recurrence of manic, depressive and mixed episodes in bipolar disorder, patients who have responded to quetiapine for acute treatment of bipolar disorder should continue therapy at the same dose. The dose may then be adjusted depending on clinical response and tolerability of the individual patient, within the range of 300 to 800 mg/day administered twice daily. It is important that the lowest effective dose is used for maintenance therapy.
Elderly
As with other antipsychotics, Quetiapine Film-coated Tablets should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on Quetiapine Film-coated tablets 25 mg/day. The dose should be increased daily in increments of 25 to 50 mg, to an effective dose, which is likely to be lower than that in younger patients.

Efficacy and safety have not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Children and adolescents
Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in sections 4.4, 4.8, 5.1 and 5.2.

Renal impairment
Dose adjustment is not necessary in patients with renal impairment.

Hepatic impairment
Quetiapine is extensively metabolised by the liver. Therefore, quetiapine should be used with caution in patients with known hepatic impairment, especially during the initial dose titration period. Patients with known hepatic impairment should be started with 25 mg/day. The dosage should be increased daily with increments of 25 - 50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.

4.3 CONTRAINDICATIONS
Quetiapine film-coated tablets are contraindicated in patients who are hypersensitive to any component of this product.

Concomitant administration of cytochrome P450 3A4 inhibitors such as HIV protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated. (See also section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Children and adolescents (10 to 17 years of age)
Quetiapine Film-coated tablets are not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials have shown that in addition to the known safety profile identified in adults (see section 4.8 Undesirable effects), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, and extrapyramidal symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

Furthermore, the long-term safety implications of treatment on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

In placebo-controlled clinical trials with children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia and bipolar mania (see section 4.8 Undesirable effects).

Suicide/suicidal thoughts or clinical worsening
Depression in bipolar disorder is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

In clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients less than 25 years of age who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively).
**Somnolence**  
Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see Section 4.8 Undesirable effects). In clinical trials for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

**Cardiovascular disease**  
Quetiapine Film-coated Tablets should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.

Quetiapine may induce orthostatic hypotension, especially during the initial dose-titration period; this is more common in elderly patients than in younger patients. Dose reduction or more gradual titration should be considered if this occurs.

**Seizures**  
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with Quetiapine or placebo. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see section 4.8 Undesirable effects).

**Extrapyramidal symptoms**  
In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder (see Section 4.8 Undesirable effects).

**Tardive dyskinesia**  
Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic drugs including quetiapine. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Quetiapine Film-coated Tablets should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see section 4.8 Undesirable effects).

**Neuroleptic malignant syndrome**  
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including Quetiapine Film-coated Tablets (see Section 4.8 Undesirable effects). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, Quetiapine Film-coated Tablets should be discontinued and appropriate medical treatment given.

**Severe neutropenia**  
Severe neutropenia (neutrophil count < 0.5 X 10^9/L) has been uncommonly reported in quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with Quetiapine. There was no apparent dose relationship. During post-marketing experience, resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count < 1.0 X 10^9/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X 10^9/L). (See section 5.1 Pharmacodynamic properties).

**Interactions**  
See also Section 4.5 Interactions with other medicinal products and other forms of interaction.

Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer treatment. It is important that any change in the inducer treatment is gradual, and if required, inducer may be replaced with a non-inducer (e.g. sodium valproate).
Hyperglycaemia
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported during treatment with quetiapine. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

Lipids
Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8 Undesirable effects). Lipid changes should be managed as clinically appropriate.

QT prolongation
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT interval. However, with overdose (see section 4.9) QT prolongation was observed. As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when quetiapine is prescribed with medicines known to increase QTc interval, and concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Acute withdrawal reactions
Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability have been described after abrupt cessation of quetiapine. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Gradual withdrawal over a period of at least one to two weeks is advisable (see Section 4.8 Undesirable effects).

Elderly with dementia-related psychosis
Quetiapine is not approved for the treatment of patients with dementia-related psychosis.

An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomized placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with an increased risk of stroke.

In a meta-analysis of atypical antipsychotic drugs, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. However in two 10-week placebo-controlled quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% compared to 3.2% in the placebo group. The patients in these trials died of a variety of causes that were consistent with expectations for this population. These data do not show causal relationship between quetiapine treatment and death in elderly patients with dementia.

Hepatic effects
If jaundice develops, Quetiapine film-coated tablets should be discontinued.

Concomitant illness
Dysphagia (see Section 4.8 Undesirable effects) and aspiration have been reported with Quetiapine. Although a causal relationship with aspiration pneumonia has not been established, Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures undertaken.

Lactose
Quetiapine Film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.
Additional information
Quetiapine data in combination with divalproex (valproate semisodium) or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 Undesirable effects and 5.1 Pharmacodynamic properties). The data showed an additive effect at week 3.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Given the primary central nervous system effects of quetiapine, it should be used with caution in combination with other centrally acting drugs and alcohol.

Cytochrome P450 (CYP) 3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine and a CYP3A4 inhibitor is contraindicated. It is also not recommended to take quetiapine together with grapefruit juice.

Quetiapine did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. However, in a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur which can influence the effect of quetiapine therapy. Co-administration of quetiapine and phenytoin (microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approximately 45%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine therapy should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer treatment is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate) (see also section 4.4 Special warnings and special precautions for use).

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 inhibitor).

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However co-administration of quetiapine and thioridazine caused increases in the clearance of quetiapine of about 70%.

The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine, a known P450 enzyme inhibitor.

The pharmacokinetics of lithium were not altered when co-administered with quetiapine.

The pharmacokinetics of valproic acid and quetiapine were not altered to a clinically relevant extent when co-administered as valproate semisodium (also known as divalproex sodium (USAN)) and Quetiapine film-coated tablets (quetiapine fumarate). Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.

Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QTc interval.

4.6 PREGNANCY AND LACTATION
The safety and efficacy of quetiapine during human pregnancy have not yet been established. Up to now there are no indications for harmfulness in animal tests, possible effects on the foetal eye have not been examined though. Therefore, Quetiapine should only be used during pregnancy if the benefits justify the potential risks. Following pregnancies in which Quetiapine was used, neonatal withdrawal symptoms were observed.
The degree to which quetiapine is excreted into human milk is unknown. Women who are breast feeding should therefore be advised to avoid breast feeding while taking Quetiapine Film-coated Tablets.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness and may cause somnolence. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility to this is known.

4.8 UNDESIRABLE EFFECTS
The most commonly reported Adverse Drug Reactions (ADRs) with Quetiapine Film-coated Tablets are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension, and dyspepsia.

As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with Quetiapine Film-coated Tablets.

The incidences of ADRs associated with quetiapine therapy, are tabulated below according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

Blood and lymphatic system disorders
Common: Leucopenia
Uncommon: Eosinophilia, Thrombocytopenia
Unknown: Neutropenia

Immune system disorders
Uncommon: Hypersensitivity
Very rare: Anaphylactic reaction

Endocrine disorders
Common: Hyperprolactinaemia

Metabolism and nutritional disorders
Common: Increased appetite
Very rare: Diabetes Mellitus

Psychiatric disorders
Common: Abnormal dreams and nightmares

Nervous system disorders
Very Common: Dizziness, somnolence, headache
Common: Syncope, Extrapyramidal symptoms, Dysarthria
Uncommon: Seizure, Restless leg syndrome, Tardive dyskinesia

Cardiac disorders
Common: Tachycardia
Eye disorders
Common: Vision blurred

Vascular disorders
Common: Orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Common: Rhinitis

Gastrointestinal disorders
Very Common: Dry mouth
Common: Constipation, dyspepsia
Uncommon: Dysphagia

Hepato-biliary disorders
Rare: Jaundice
Very rare: Hepatitis

Skin and subcutaneous tissue disorders
Very rare: Angioedema, Stevens-Johnson syndrome

Reproductive system and breast disorders
Rare: Priapism, galactorrhoea

General disorders and administration site conditions
Very Common: Withdrawal (discontinuation) symptoms
Common: Mild asthenia, peripheral oedema, irritability
Rare: Neuroleptic malignant syndrome

Investigations
Very Common: Elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain
Common: Elevations in serum transaminases (ALT, AST), decreased neutrophil count, blood glucose increased to hyperglycaemic levels
Uncommon: Elevations in gamma-GT levels, platelet count decreased
Rare: Elevations in blood creatine phosphokinase, Venous thromboembolism

(1) See section 4.4 Special Warnings and Special Precautions for Use.

(2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of SEROQUEL.

(3) Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT levels have been observed in some patients administered SEROQUEL.

(4) As with other antipsychotics with alpha, adrenergic blocking activity, SEROQUEL may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some
(5) Exacerbation of pre-existing diabetes has been reported in very rare cases.

(6) Calculation of frequency for these ADRs have been taken from post-marketing data only.

(7) Fasting blood glucose ≥ 7.0 mmol/L or a non fasting blood glucose ≥ 11.1 mmol/L on at least one occasion.

(8) An increase in the rate of dysphagia with SEROQUEL vs. placebo was only observed in the clinical trials in bipolar depression.

(9) Based on > 7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.

(10) The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.

(11) Triglycerides ≥ 200 mg/dL (≥ 2.258 mmol/L) (patients ≥ 18 years of age) or ≥ 150 mg/dL (≥ 1.694 mmol/L) (patients < 18 years of age) on at least one occasion.

(12) Cholesterol ≥ 240 mg/dL (≥ 6.2064 mmol/L) (patients ≥ 18 years of age) or ≥ 200 mg/dL (≥ 5.172 mmol/L) (patients < 18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥ 30 mg/dL (≥ 0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥ 1.07 mmol/L).

(13) See text below.

(14) Platelets ≥ 100 x 10^9/L on at least one occasion.

(15) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.

(16) Prolactin levels (patients > 18 years of age): ≥ 20 μg/L (> 869.56 pmol/L) males; ≥ 30 μg/L (> 1304.34 pmol/L) females at any time.

(17) May lead to falls.

(18) HDL cholesterol: < 40 mg/dL (1.025 mmol/L) males; < 50 mg/dL (1.282 mmol/L) females at any time.

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported with the use of neuroleptics and are considered class effects (see Section 4.4 Special warnings and special precautions for use).

In short-term, placebo-controlled clinical trials in bipolar depression the aggregated incidence of extrapyramidal symptoms was 8.9% for Quetiapine compared to 3.8% for placebo, though the incidence of the individual adverse events were generally low and did not exceed 4% in any treatment group. In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for Quetiapine and 8.0% for placebo; bipolar mania: 11.2% for Quetiapine and 11.4% for placebo).

Quetiapine treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T₄ and free T₄. The reduction in total and free T₄ was maximal within the first two to four weeks of quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T₄, irrespective of the duration of treatment. Smaller decreases in total T₃ and reverse T₃ were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal
increases in TSH were not observed, with no indication that quetiapine causes clinically relevant hypothyroidism.

4.9 OVERDOSE
Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of quetiapine alone. However, survival has also been reported following acute overdoses of up to 30 grams.

In post-marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma or QT-prolongation.

In general, reported signs and symptoms were those resulting from an exaggeration of the known pharmacological effects of the active substance, i.e. drowsiness and sedation, tachycardia and hypotension.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See section 4.4 : Special warnings and special precautions for use: Cardiovascular).

Management
There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal should be considered.

Close medical supervision and monitoring should be continued until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic Group: Antipsychotics
Therapeutic classification: N05AH04

Mechanism of action
Quetiapine is an atypical antipsychotic agent. Quetiapine and the active metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit an affinity for brain serotonin (5HT2) and dopamine D1 and D2 receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT2 relative to D2 receptors which is believed to contribute to the antipsychotic properties and low extrapyramidal symptoms (EPS) liability of quetiapine compared to typical antipsychotics. Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity for adrenergic α2-receptors and serotonin 5HT1A receptors.
Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

Pharmacodynamic effect
Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D2-receptor blockade. In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D2 receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D2 receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration. The extent to which the norquetiapine metabolite contributes to the pharmacological activity of Quetiapine in humans is not known.
Clinical Efficacy

The results of three placebo-controlled clinical trials in patients with schizophrenia, including one that used a dose range of Quetiapine of 75 to 750 mg/day, identified no difference between Quetiapine and placebo in the incidence of EPS or use of concomitant anticholinergics. In four controlled trials, evaluating doses of Quetiapine up to 800 mg for the treatment of bipolar mania, two each in monotherapy and as adjunct therapy to lithium or valproate semisodium, there were no differences between the Quetiapine and placebo treatment groups in the incidence of EPS or concomitant use of anticholinergics.

In clinical trials, Quetiapine has been shown to be effective in the treatment of both positive and negative symptoms of schizophrenia. In one trial against chlorpromazine, and two against haloperidol, Quetiapine showed similar short-term efficacy.

In clinical trials, Quetiapine has been shown to be effective as monotherapy or as adjunct therapy in reducing manic symptoms in patients with bipolar mania. The mean last week median dose of Quetiapine in responders, was approximately 600 mg and approximately 85% of the responders were in the dose range of 400 to 800 mg per day.

In 4 clinical trials in patients with depressive episodes in bipolar I or bipolar II disorder, with and without rapid cycling courses, 51% of quetiapine treated patients had at least a 50% improvement in MADRS total score at week 8 compared to 37% of the placebo treated patients. The anti-depressant effect was significant at Day 8 (week 1). There were fewer episodes of treatment-emergent mania with Quetiapine than with placebo. In continuation treatment the anti-depressant effect was maintained for patients on Quetiapine (mean duration of treatment 30 weeks). Quetiapine reduced the risk of a recurrent mood (manic and depressed) event by 49%. Quetiapine was superior to placebo in treating the anxiety symptoms associated with bipolar depression as assessed by mean change from baseline to week 8 in HAM-A total score.

In one long-term study (up to 2 years treatment, mean quetiapine exposure 191 days) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed), in patients with bipolar I disorder. The number of patients with a mood event was 91 (22.5%) in the quetiapine group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups respectively. In patients who responded to quetiapine, when comparing continued treatment with quetiapine to switching to lithium, the results indicated that a switch to lithium treatment does not appear to be associated with an increased time to recurrence of a mood event. In two recurrence prevention studies evaluating Quetiapine in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with Quetiapine was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). The risk of a recurrent event was reduced by 70%. Quetiapine was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In placebo-controlled monotherapy trials in patients with a baseline neutrophil count \(\geq 1.5 \times 10^9/L\), the incidence of at least one occurrence of neutrophil count \(<1.5 \times 10^9/L\), was 1.72% in patients treated with Quetiapine compared to 0.73% in placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator; patients with a baseline neutrophil count \(\geq 1.5 \times 10^9/L\), the incidence of at least one occurrence of neutrophil count \(<0.5 \times 10^9/L\), was 0.21% in patients treated with Quetiapine and 0% in placebo treated patients and the incidence \(>0.5 - <1.0 \times 10^9/L\), was 0.75% in patients treated with Quetiapine and 0.11% in placebo-treated patients.

Children and adolescents (10 to 17 years of age)

The efficacy and safety of Quetiapine was studied in a 3-week placebo controlled study for the treatment of mania (n= 284 patients from the US, aged 10-17). About 45% of the patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo controlled study for the treatment of schizophrenia (n = 222 patients, aged 13-17) was performed. In both studies, patients with known lack of response to Quetiapine were excluded. Treatment with Quetiapine was initiated at 50 mg/day and on day 2 increased to 100 mg/day; subsequently the dose was titrated to a target dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day) using increments of 100 mg/day given two or three times daily.
In the mania study, the difference in LS mean change from baseline in YMRS total score (active minus placebo) was –5.21 for Quetiapine 400 mg/day and –6.56 for Quetiapine 600 mg/day. Responder rates (YMRS improvement ≥50%) were 64% for Quetiapine 400 mg/day, 58% for 600 mg/day and 37% in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score (active minus placebo) was –8.16 for Quetiapine 400 mg/day and –9.29 for Quetiapine 800 mg/day. Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine was superior to placebo with respect to the percentage of patients achieving response, defined as ≥30% reduction from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

No data are available on maintenance of effect or recurrence prevention in this age group. A 26-week open-label extension to the acute trials (n= 380 patients), with Quetiapine flexibly dosed at 400-800 mg/day, provided additional safety data. Increases in blood pressure were reported in children and adolescents and increased appetite, extrapyramidal symptoms and elevations in serum prolactin were reported with higher frequency in children and adolescents than in adult patients (see Section 4.4 Special warnings and special precautions for use and Section 4.8 Undesirable effects).

Extrapyramidal Symptoms
In a short-term placebo-controlled monotherapy trial in adolescent patients (13-17 years of age) with schizophrenia, the aggregated incidence of extrapyramidal symptoms was 12.9% for quetiapine and 5.3% for placebo, though the incidence of the individual adverse events (e.g. akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar mania, the aggregated incidence of extrapyramidal symptoms was 3.6% for quetiapine and 1.1% for placebo. In a long-term open label study of schizophrenia and bipolar mania, the aggregated incidence of treatment-emergent EPS was 10%.

Weight Gain
In short-term clinical trials in paediatric patients (10-17 years of age), 17% of quetiapine-treated patients and 2.5% of placebo-treated patients gained ≥7% of their body weight. When adjusting for normal growth over longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who were treated with quetiapine for at least 26 weeks met this criterion.

Suicide/Suicidal thoughts or Clinical worsening
In short-term placebo-controlled clinical trials in paediatric patients with schizophrenia, the incidence of suicide related events was 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients <18 years of age. In short-term placebo-controlled trials in paediatric patients with bipolar mania, the incidence of suicide related events was 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients <18 years of age.

5.2 PHARMACOKINETIC PROPERTIES
Quetiapine is well absorbed and extensively metabolised following oral administration. The bioavailability of quetiapine is not significantly affected by administration with food. Quetiapine is approximately 83% bound to plasma proteins. Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine. The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. Clinical trials have demonstrated that Quetiapine is effective when given twice a day. This is further supported by data from a positron emission tomography (PET) study which identified that 5HT2 and D2 receptor occupancy are maintained for up to 12 hours after dosing with quetiapine. The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range. The kinetics of quetiapine do not differ between men and women. The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73m²), but the individual clearance values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.
Quetiapine is extensively metabolised, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces. The mean quetiapine plasma clearance decreases by approx. 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see section 4.2 Posology and method of administration). 

*In vitro* investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

In a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of quetiapine given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean $C_{\text{max}}$ and AUC of quetiapine of 235% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%. The mean half-life of quetiapine increased from 2.6 to 6.8 hours, but the mean $t_{\text{max}}$ was unchanged.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these *in vitro* results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

**Children and adolescents (10 to 17 years of age)**

Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though $C_{\text{max}}$ in children was at the higher end of the range observed in adults. The AUC and $C_{\text{max}}$ for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

5.3 PRECLINICAL SAFETY DATA

There was no evidence of genotoxicity in a series of *in vitro* and *in vivo* genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in long-term clinical research:

In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy, a lowering in plasma T₃ levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts.

Taking these findings into consideration, the benefits of the treatment with quetiapine need to be balanced against the safety risks for the patient.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

**Core**

- Microcrystalline cellulose
- Povidone K29-32
- Calcium hydrogen phosphate dihydrate
- Sodium starch glycolate (Type A)
- Lactose monohydrate
- Magnesium stearate

**Film-coat**

- Opadry II Yellow 33G32578 containing:
  - Hypermellose 6cP
Titanium dioxide
Lactose monohydrate
Macrogol 3350
Triacetin
Iron oxide yellow (E172)

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions

6.5 NATURE AND CONTENTS OF CONTAINER
Blisters (PVC/PVDC/Al and PVC/Al) Pack sizes: 6, 10, 20, 30, 50, 60, 90, 100 tablets*
Plastic (polyethylene) tablet containers Pack sizes: 6, 10, 20, 30, 50, 60, 90, 100 tablets*
* Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0164

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/02/2011

10 DATE OF REVISION OF THE TEXT
25/02/2011
1 NAME OF THE MEDICINAL PRODUCT
Quetiapine 150mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 150mg quetiapine (as fumarate).

Excipients:
Each tablet contains 31.05 mg lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Pale yellow, 6.9 x 13.8 mm, oval, biconvex, engraved with Q on one side

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Quetiapine is indicated for the treatment of:
Schizophrenia.

Bipolar disorder including:
- manic episodes associated with bipolar disorder
- major depressive episodes in bipolar disorder
- preventing recurrence in bipolar disorder in patients whose manic, mixed or depressive episode has responded to quetiapine treatment.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Quetiapine Film-coated Tablets can be administered with or without food.

Adults
For the treatment of schizophrenia: Quetiapine should be administered twice a day. The total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4).

From Day 4 onwards, the dose should be titrated to the usual effective dose range of 300 to 450 mg/day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 to 750 mg/day.

For the treatment of manic episodes associated with bipolar disorder: Quetiapine should be administered twice a day. As monotherapy or as adjunct to mood stabilisers, the total daily dose for the first four days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg per day by Day 6 should be in increments of no greater than 200 mg per day.

The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg per day. The usual effective dose is in the range of 400 to 800 mg per day.

For the treatment of depressive episodes in bipolar disorder: Quetiapine should be administered once daily at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group. Individual patients may benefit from a 600 mg dose. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered. When treating depressive episodes in bipolar disorder, treatment should be initiated by physicians experienced in treating bipolar disorder.

For preventing recurrence in bipolar disorder: For prevention of recurrence of manic, depressive and mixed episodes in bipolar disorder, patients who have responded to quetiapine for acute treatment of bipolar disorder should continue therapy at the same dose. The dose may then be adjusted depending on clinical response and tolerability of the individual patient, within the range of 300 to 800 mg/day administered twice daily. It is important that the lowest effective dose is used for maintenance therapy.
**Elderly**
As with other antipsychotics, Quetiapine Film-coated Tablets should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on Quetiapine Film-coated tablets 25 mg/day. The dose should be increased daily in increments of 25 to 50 mg, to an effective dose, which is likely to be lower than that in younger patients.

Efficacy and safety have not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

**Children and adolescents**
Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in sections 4.4, 4.8, 5.1 and 5.2.

**Renal impairment**
Dose adjustment is not necessary in patients with renal impairment.

**Hepatic impairment**
Quetiapine is extensively metabolised by the liver. Therefore, quetiapine should be used with caution in patients with known hepatic impairment, especially during the initial dose titration period. Patients with known hepatic impairment should be started with 25 mg/day. The dosage should be increased daily with increments of 25 - 50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.

4.3 CONTRAINDICATIONS
Quetiapine film-coated tablets are contraindicated in patients who are hypersensitive to any component of this product.

Concomitant administration of cytochrome P450 3A4 inhibitors such as HIV protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated. (See also section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
**Children and adolescents (10 to 17 years of age)**
Quetiapine Film-coated tablets are not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials have shown that in addition to the known safety profile identified in adults (see section 4.8 Undesirable effects), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, and extrapyramidal symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

Furthermore, the long-term safety implications of treatment on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

In placebo-controlled clinical trials with children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia and bipolar mania (see section 4.8 Undesirable effects).

**Suicide/suicidal thoughts or clinical worsening**
Depression in bipolar disorder is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

In clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients less than 25 years of age who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively).
Somnolence
Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see Section 4.8 Undesirable effects). In clinical trials for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

Cardiovascular disease
Quetiapine Film-coated Tablets should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.

Quetiapine may induce orthostatic hypotension, especially during the initial dose-titration period; this is more common in elderly patients than in younger patients. Dose reduction or more gradual titration should be considered if this occurs.

Seizures
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with Quetiapine or placebo. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see section 4.8 Undesirable effects).

Extrapyramidal symptoms
In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder (see Section 4.8 Undesirable effects).

Tardive dyskinesia
Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic drugs including quetiapine. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Quetiapine Film-coated Tablets should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see section 4.8 Undesirable effects).

Neuroleptic malignant syndrome
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including Quetiapine Film-coated Tablets (see Section 4.8 Undesirable effects). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, Quetiapine Film-coated Tablets should be discontinued and appropriate medical treatment given.

Severe neutropenia
Severe neutropenia (neutrophil count < 0.5 X 10^9/L) has been uncommonly reported in quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with Quetiapine. There was no apparent dose relationship. During post-marketing experience, resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count < 1.0 X 10^9/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X 10^9/L). (See section 5.1 Pharmacodynamic properties).

Interactions
See also Section 4.5 Interactions with other medicinal products and other forms of interaction.

Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer treatment. It is important that any change in the inducer treatment is gradual, and if required, inducer may be replaced with a non-inducer (e.g. sodium valproate).
Hyperglycaemia
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported during treatment with quetiapine. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

Lipids
Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8 Undesirable effects). Lipid changes should be managed as clinically appropriate.

QT prolongation
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT interval. However, with overdose (see section 4.9) QT prolongation was observed. As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when quetiapine is prescribed with medicines known to increase QTc interval, and concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Acute withdrawal reactions
Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability have been described after abrupt cessation of quetiapine. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Gradual withdrawal over a period of at least one to two weeks is advisable (see Section 4.8 Undesirable effects).

Elderly with dementia-related psychosis
Quetiapine is not approved for the treatment of patients with dementia-related psychosis.

An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomized placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with an increased risk of stroke.

In a meta-analysis of atypical antipsychotic drugs, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. However in two 10-week placebo-controlled quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% compared to 3.2% in the placebo group. The patients in these trials died of a variety of causes that were consistent with expectations for this population. These data do not show causal relationship between quetiapine treatment and death in elderly patients with dementia.

Hepatic effects
If jaundice develops, Quetiapine film-coated tablets should be discontinued.

Concomitant illness
Dysphagia (see Section 4.8 Undesirable effects) and aspiration have been reported with Quetiapine. Although a causal relationship with aspiration pneumonia has not been established, Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures undertaken.

Lactose
Quetiapine Film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.
Additional information
Quetiapine data in combination with divalproex (valproate semisodium) or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 Undesirable effects and 5.1 Pharmacodynamic properties). The data showed an additive effect at week 3.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Given the primary central nervous system effects of quetiapine, it should be used with caution in combination with other centrally acting drugs and alcohol.

Cytochrome P450 (CYP) 3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine and a CYP3A4 inhibitor is contraindicated. It is also not recommended to take quetiapine together with grapefruit juice.

Quetiapine did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. However, in a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur which can influence the effect of quetiapine therapy. Co-administration of quetiapine and phenytoin (microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approximately 450%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine therapy should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer treatment is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate) (see also section 4.4 Special warnings and special precautions for use).

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 inhibitor).

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However co-administration of quetiapine and thioridazine caused increases in the clearance of quetiapine of about 70%.

The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine, a known P450 enzyme inhibitor.

The pharmacokinetics of lithium were not altered when co-administered with quetiapine.

The pharmacokinetics of valproic acid and quetiapine were not altered to a clinically relevant extent when co-administered as valproate semisodium (also known as divalproex sodium (USAN)) and Quetiapine film-coated tablets (quetiapine fumarate). Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.

Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QTc interval.

4.6 PREGNANCY AND LACTATION
The safety and efficacy of quetiapine during human pregnancy have not yet been established. Up to now there are no indications for harmfulness in animal tests, possible effects on the foetal eye have not been examined though. Therefore, Quetiapine should only be used during pregnancy if the benefits justify the potential risks. Following pregnancies in which Quetiapine was used, neonatal withdrawal symptoms were observed.
The degree to which quetiapine is excreted into human milk is unknown. Women who are breast feeding should therefore be advised to avoid breast feeding while taking Quetiapine Film-coated Tablets.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness and may cause somnolence. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility to this is known.

4.8 UNDESIRABLE EFFECTS
The most commonly reported Adverse Drug Reactions (ADRs) with Quetiapine Film-coated Tablets are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension, and dyspepsia.

As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with Quetiapine Film-coated Tablets.

The incidences of ADRs associated with quetiapine therapy, are tabulated below according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

**Blood and lymphatic system disorders**
- **Common:** Leucopenia
- **Uncommon:** Eosinophilia, Thrombocytopenia
- **Unknown:** Neutropenia

**Immune system disorders**
- **Uncommon:** Hypersensitivity
- **Very rare:** Anaphylactic reaction

**Endocrine disorders**
- **Common:** Hyperprolactinaemia

**Metabolism and nutritional disorders**
- **Common:** Increased appetite
- **Very rare:** Diabetes Mellitus

**Psychiatric disorders**
- **Common:** Abnormal dreams and nightmares

**Nervous system disorders**
- **Very Common:** Dizziness, somnolence, headache
- **Common:** Syncope, Extrapyramidal symptoms, Dysarthria
- **Uncommon:** Seizure, Restless leg syndrome, Tardive dyskinesia

**Cardiac disorders**
- **Common:** Tachycardia
Eye disorders
Common: Vision blurred

Vascular disorders
Common: Orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Common: Rhinitis

Gastrointestinal disorders
Very Common: Dry mouth
Common: Constipation, dyspepsia
Uncommon: Dysphagia

Hepato-biliary disorders
Rare: Jaundice
Very rare: Hepatitis

Skin and subcutaneous tissue disorders
Very rare: Angioedema, Stevens-Johnson syndrome

Reproductive system and breast disorders
Rare: Priapism, galactorrhoea

General disorders and administration site conditions
Very Common: Withdrawal (discontinuation) symptoms
Common: Mild asthenia, peripheral oedema, irritability
Rare: Neuroleptic malignant syndrome

Investigations
Very Common: Elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain
Common: Elevations in serum transaminases (ALT, AST), decreased neutrophil count, blood glucose increased to hyperglycaemic levels
Uncommon: Elevations in gamma-GT levels, platelet count decreased
Rare: Elevations in blood creatine phosphokinase, Venous thromboembolism

(1) See section 4.4 Special Warnings and Special Precautions for Use.

(2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of SEROQUEL.

(3) Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT levels have been observed in some patients administered SEROQUEL.

(4) As with other antipsychotics with alpha, adrenergic blocking activity, SEROQUEL may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some
patients, syncope, especially during the initial dose-titration period. (See section 4.4 Special warnings and special precautions for use).

(5) Exacerbation of pre-existing diabetes has been reported in very rare cases.

(6) Calculation of frequency for these ADRs have been taken from post-marketing data only.

(7) Fasting blood glucose ≥ 7.0 mmol/L or a non fasting blood glucose ≥ 11.1 mmol/L on at least one occasion.

(8) An increase in the rate of dysphagia with SEROQUEL vs. placebo was only observed in the clinical trials in bipolar depression.

(9) Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.

(10) The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.

(11) Triglycerides ≥ 200 mg/dL (≥ 2.258 mmol/L) (patients ≥ 18 years of age) or ≥ 150 mg/dL (≥ 1.694 mmol/L) (patients <18 years of age) on at least one occasion.

(12) Cholesterol ≥ 240 mg/dL (≥ 6.2064 mmol/L) (patients ≥ 18 years of age) or ≥ 200 mg/dL (≥ 5.172 mmol/L) (patients <18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥ 30 mg/dL (≥ 0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥ 1.07 mmol/L).

(13) See text below.

(14) Platelets ≥ 100 x 10^9/L on at least one occasion.

(15) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.

(16) Prolactin levels (patients>18 years of age):>20 μg/L (>869.56 pmol/L) males;>30 μg/L (>1304.34 pmol/L) females at any time.

(17) May lead to falls.

(18) HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported with the use of neuroleptics and are considered class effects (see Section 4.4 Special warnings and special precautions for use).

In short-term, placebo-controlled clinical trials in bipolar depression the aggregated incidence of extrapyramidal symptoms was 8.9% for Quetiapine compared to 3.8% for placebo, though the incidence of the individual adverse events were generally low and did not exceed 4% in any treatment group. In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for Quetiapine and 8.0% for placebo; bipolar mania: 11.2% for Quetiapine and 11.4% for placebo).

Quetiapine treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T4 and free T4. The reduction in total and free T4 was maximal within the first two to four weeks of quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. Smaller decreases in total T3 and reverse T3 were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal
increases in TSH were not observed, with no indication that quetiapine causes clinically relevant hypothyroidism.

4.9 OVERDOSE
Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of quetiapine alone. However, survival has also been reported following acute overdoses of up to 30 grams.

In post-marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma or QT-prolongation.

In general, reported signs and symptoms were those resulting from an exaggeration of the known pharmacological effects of the active substance, i.e. drowsiness and sedation, tachycardia and hypotension.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See section 4.4 : Special warnings and special precautions for use: Cardiovascular).

Management
There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal should be considered.

Close medical supervision and monitoring should be continued until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic Group: Antipsychotics
Therapeutic classification: N05AH04

Mechanism of action
Quetiapine is an atypical antipsychotic agent. Quetiapine and the active metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit an affinity for brain serotonin (5HT2) and dopamine D1 and D2 receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT2 relative to D2 receptors which is believed to contribute to the antipsychotic properties and low extrapyramidal symptoms (EPS) liability of quetiapine compared to typical antipsychotics. Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity for adrenergic α2-receptors and serotonin 5HT1A receptors.
Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

Pharmacodynamic effect
Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D2-receptor blockade. In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D2 receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D2 receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration. The extent to which the norquetiapine metabolite contributes to the pharmacological activity of Quetiapine in humans is not known.
Clinical Efficacy
The results of three placebo-controlled clinical trials in patients with schizophrenia, including one that used a dose range of Quetiapine of 75 to 750 mg/day, identified no difference between Quetiapine and placebo in the incidence of EPS or use of concomitant anticholinergics.

In four controlled trials, evaluating doses of Quetiapine up to 800 mg for the treatment of bipolar mania, two each in monotherapy and as adjunct therapy to lithium or valproate semisodium, there were no differences between the Quetiapine and placebo treatment groups in the incidence of EPS or concomitant use of anticholinergics.

In clinical trials, Quetiapine has been shown to be effective in the treatment of both positive and negative symptoms of schizophrenia. In one trial against chlorpromazine, and two against haloperidol, Quetiapine showed similar short-term efficacy.

In clinical trials, Quetiapine has been shown to be effective as monotherapy or as adjunct therapy in reducing manic symptoms in patients with bipolar mania. The mean last week median dose of Quetiapine in responders, was approximately 600 mg and approximately 85% of the responders were in the dose range of 400 to 800 mg per day.

In 4 clinical trials in patients with depressive episodes in bipolar I or bipolar II disorder, with and without rapid cycling courses, 51% of quetiapine treated patients had at least a 50% improvement in MADRS total score at week 8 compared to 37% of the placebo treated patients. The anti-depressant effect was significant at Day 8 (week 1). There were fewer episodes of treatment-emergent mania with Quetiapine than with placebo. In continuation treatment the anti-depressant effect was maintained for patients on Quetiapine (mean duration of treatment 30 weeks). Quetiapine reduced the risk of a recurrent mood (manic and depressed) event by 49%. Quetiapine was superior to placebo in treating the anxiety symptoms associated with bipolar depression as assessed by mean change from baseline to week 8 in HAM-A total score.

In one long-term study (up to 2 years treatment, mean quetiapine exposure 191 days) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed), in patients with bipolar I disorder. The number of patients with a mood event was 91 (22.5%) in the quetiapine group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups respectively. In patients who responded to quetiapine, when comparing continued treatment with quetiapine to switching to lithium, the results indicated that a switch to lithium treatment does not appear to be associated with an increased time to recurrence of a mood event. In two recurrence prevention studies evaluating Quetiapine in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with Quetiapine was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). The risk of a recurrent event was reduced by 70%. Quetiapine was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In placebo-controlled monotherapy trials in patients with a baseline neutrophil count $\geq 1.5 \times 10^9$/$L$, the incidence of at least one occurrence of neutrophil count $<1.5 \times 10^9$/$L$, was 1.72% in patients treated with Quetiapine compared to 0.73% in placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator; patients with a baseline neutrophil count $\geq 1.5 \times 10^9$/$L$), the incidence of at least one occurrence of neutrophil count $<0.5 \times 10^9$/$L$ was 0.21% in patients treated with Quetiapine and 0% in placebo treated patients and the incidence $0.5 - <1.0 \times 10^9$/$L$ was 0.75% in patients treated with Quetiapine and 0.11% in placebo-treated patients.

Children and adolescents (10 to 17 years of age)
The efficacy and safety of Quetiapine was studied in a 3-week placebo controlled study for the treatment of mania ($n=284$ patients from the US, aged 10-17). About 45% of the patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo controlled study for the treatment of schizophrenia ($n=222$ patients, aged 13-17) was performed. In both studies, patients with known lack of response to Quetiapine were excluded. Treatment with Quetiapine was initiated at 50 mg/day and on day 2 increased to 100 mg/day; subsequently the dose was titrated to a target dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day) using increments of 100 mg/day given two or three times daily.
In the mania study, the difference in LS mean change from baseline in YMRS total score (active minus placebo) was –5.21 for Quetiapine 400 mg/day and –6.56 for Quetiapine 600 mg/day. Responder rates (YMRS improvement ≥ 50%) were 64% for Quetiapine 400 mg/day, 58% for 600 mg/day and 37% in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score (active minus placebo) was –8.16 for Quetiapine 400 mg/day and –9.29 for Quetiapine 800 mg/day. Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine was superior to placebo with respect to the percentage of patients achieving response, defined as ≥ 30% reduction from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

No data are available on maintenance of effect or recurrence prevention in this age group. A 26-week open-label extension to the acute trials (n= 380 patients), with Quetiapine flexibly dosed at 400-800 mg/day, provided additional safety data. Increases in blood pressure were reported in children and adolescents and increased appetite, extrapyramidal symptoms and elevations in serum prolactin were reported with higher frequency in children and adolescents than in adult patients (see Section 4.4 Special warnings and special precautions for use and Section 4.8 Undesirable effects).

Extrapyramidal Symptoms
In a short-term placebo-controlled monotherapy trial in adolescent patients (13-17 years of age) with schizophrenia, the aggregated incidence of extrapyramidal symptoms was 12.9% for quetiapine and 5.3% for placebo, though the incidence of the individual adverse events (e.g. akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar mania, the aggregated incidence of extrapyramidal symptoms was 3.6% for quetiapine and 1.1% for placebo. In a long-term open label study of schizophrenia and bipolar mania, the aggregated incidence of treatment-emergent EPS was 10%.

Weight Gain
In short-term clinical trials in paediatric patients (10-17 years of age), 17% of quetiapine-treated patients and 2.5% of placebo-treated patients gained 2 7% of their body weight. When adjusting for normal growth over longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who were treated with quetiapine for at least 26 weeks met this criterion.

Suicide/Suicidal thoughts or Clinical worsening
In short-term placebo-controlled clinical trials in paediatric patients with schizophrenia, the incidence of suicide related events was 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients <18 years of age. In short-term placebo-controlled trials in paediatric patients with bipolar mania, the incidence of suicide related events was 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients <18 years of age.

5.2 PHARMACOKINETIC PROPERTIES
Quetiapine is well absorbed and extensively metabolised following oral administration. The bioavailability of quetiapine is not significantly affected by administration with food. Quetiapine is approximately 83% bound to plasma proteins. Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine. The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively.

Clinical trials have demonstrated that Quetiapine is effective when given twice a day. This is further supported by data from a positron emission tomography (PET) study which identified that 5HT2 and D2 receptor occupancy are maintained for up to 12 hours after dosing with quetiapine. The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range. The kinetics of quetiapine do not differ between men and women. The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73m²), but the individual clearance
values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Quetiapine is extensively metabolised, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces. The mean quetiapine plasma clearance decreases by approx. 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see section 4.2 Posology and method of administration).

In vivo investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

In a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of quetiapine given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean C\text{max} and AUC of quetiapine of 235% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%. The mean half-life of quetiapine increased from 2.6 to 6.8 hours, but the mean t\text{max} was unchanged.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Children and adolescents (10 to 17 years of age)
Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though C\text{max} in children was at the higher end of the range observed in adults. The AUC and C\text{max} for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

5.3 PRECLINICAL SAFETY DATA
There was no evidence of genotoxicity in a series of in vitro and in vivo genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in long-term clinical research:

In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy, a lowering in plasma T3 levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts.

Taking these findings into consideration, the benefits of the treatment with quetiapine need to be balanced against the safety risks for the patient.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Core
Microcrystalline cellulose
Povidone K29-32
Calcium hydrogen phosphate dihydrate
Sodium starch glycolate (Type A)
Lactose monohydrate
Magnesium stearate
Film-coat
Opadry II Yellow 33G32605 containing:
Hypermellose 6cP
Titanium dioxide
Lactose monohydrate
Macrogol 3350
Triacetin
Iron oxide yellow (E172)

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions

6.5 NATURE AND CONTENTS OF CONTAINER
Blisters (PVC/PVDC/Al and PVC/Al) Pack sizes: 6, 10, 20, 30, 50, 60, 90, 100 tablets*
Plastic (polyethylene) tablet containers Pack sizes: 6, 10, 20, 30, 50, 60, 90, 100 tablets*
* Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0165

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/02/2011

10 DATE OF REVISION OF THE TEXT
25/02/2011
1 NAME OF THE MEDICINAL PRODUCT
Quetiapine 200mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 200mg quetiapine (as fumarate).

Excipients:
Each tablet contains 41.40 mg lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
White, 16 x 8.2 mm, oval, biconvex, engraved with Q on one side

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Quetiapine is indicated for the treatment of:
Schizophrenia.

Bipolar disorder including:
- manic episodes associated with bipolar disorder
- major depressive episodes in bipolar disorder
- preventing recurrence in bipolar disorder in patients whose manic, mixed or depressive episode has responded to quetiapine treatment.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Quetiapine Film-coated Tablets can be administered with or without food.
Adults
For the treatment of schizophrenia: Quetiapine should be administered twice a day. The total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4).

From Day 4 onwards, the dose should be titrated to the usual effective dose range of 300 to 450 mg/day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 to 750 mg/day.

For the treatment of manic episodes associated with bipolar disorder: Quetiapine should be administered twice a day. As monotherapy or as adjunct to mood stabilisers, the total daily dose for the first four days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg per day by Day 6 should be in increments of no greater than 200 mg per day.

The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg per day. The usual effective dose is in the range of 400 to 800 mg per day.

For the treatment of depressive episodes in bipolar disorder: Quetiapine should be administered once daily at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group. Individual patients may benefit from a 600 mg dose. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered. When treating depressive episodes in bipolar disorder, treatment should be initiated by physicians experienced in treating bipolar disorder.

For preventing recurrence in bipolar disorder: For prevention of recurrence of manic, depressive and mixed episodes in bipolar disorder, patients who have responded to quetiapine for acute treatment of bipolar disorder should continue therapy at the same dose. The dose may then be adjusted depending on clinical response and tolerability of the individual patient, within the range of 300 to 800 mg/day administered twice daily. It is important that the lowest effective dose is used for maintenance therapy.
Elderly
As with other antipsychotics, Quetiapine Film-coated Tablets should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on Quetiapine Film-coated tablets 25 mg/day. The dose should be increased daily in increments of 25 to 50 mg, to an effective dose, which is likely to be lower than that in younger patients.

Efficacy and safety have not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Children and adolescents
Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in sections 4.4, 4.8, 5.1 and 5.2.

Renal impairment
Dose adjustment is not necessary in patients with renal impairment.

Hepatic impairment
Quetiapine is extensively metabolised by the liver. Therefore, quetiapine should be used with caution in patients with known hepatic impairment, especially during the initial dose titration period. Patients with known hepatic impairment should be started with 25 mg/day. The dosage should be increased daily with increments of 25 - 50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.

4.3 CONTRAINDICATIONS
Quetiapine film-coated tablets are contraindicated in patients who are hypersensitive to any component of this product.

Concomitant administration of cytochrome P450 3A4 inhibitors such as HIV protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated. (See also section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Children and adolescents (10 to 17 years of age)
Quetiapine Film-coated tablets are not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials have shown that in addition to the known safety profile identified in adults (see section 4.8 Undesirable effects), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, and extrapyramidal symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

Furthermore, the long-term safety implications of treatment on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

In placebo-controlled clinical trials with children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia and bipolar mania (see section 4.8 Undesirable effects).

Suicide/suicidal thoughts or clinical worsening
Depression in bipolar disorder is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

In clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients less than 25 years of age who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively).
**Somnolence**
Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see Section 4.8 Undesirable effects). In clinical trials for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

**Cardiovascular disease**
Quetiapine Film-coated Tablets should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.

Quetiapine may induce orthostatic hypotension, especially during the initial dose-titration period; this is more common in elderly patients than in younger patients. Dose reduction or more gradual titration should be considered if this occurs.

**Seizures**
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with Quetiapine or placebo. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see section 4.8 Undesirable effects).

**Extrapyramidal symptoms**
In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder (see Section 4.8 Undesirable effects).

**Tardive dyskinesia**
Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic drugs including quetiapine. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Quetiapine Film-coated Tablets should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see section 4.8 Undesirable effects).

**Neuroleptic malignant syndrome**
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including Quetiapine Film-coated Tablets (see Section 4.8 Undesirable effects). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, Quetiapine Film-coated Tablets should be discontinued and appropriate medical treatment given.

**Severe neutropenia**
Severe neutropenia (neutrophil count < 0.5 X 10^9/L) has been uncommonly reported in quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with Quetiapine. There was no apparent dose relationship. During post-marketing experience, resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count < 1.0 X 10^9/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X 10^9/L). (See section 5.1 Pharmacodynamic properties).

**Interactions**
See also Section 4.5 Interactions with other medicinal products and other forms of interaction.

Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer treatment. It is important that any change in the inducer treatment is gradual, and if required, inducer may be replaced with a non-inducer (e.g. sodium valproate).
Hyperglycaemia
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported during treatment with quetiapine. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

Lipids
Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8 Undesirable effects). Lipid changes should be managed as clinically appropriate.

QT prolongation
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT interval. However, with overdose (see section 4.9) QT prolongation was observed. As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when quetiapine is prescribed with medicines known to increase QTc interval, and concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Acute withdrawal reactions
Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability have been described after abrupt cessation of quetiapine. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Gradual withdrawal over a period of at least one to two weeks is advisable (see Section 4.8 Undesirable effects).

Elderly with dementia-related psychosis
Quetiapine is not approved for the treatment of patients with dementia-related psychosis.

An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomized placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with an increased risk of stroke.

In a meta-analysis of atypical antipsychotic drugs, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. However in two 10-week placebo-controlled quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% compared to 3.2% in the placebo group. The patients in these trials died of a variety of causes that were consistent with expectations for this population. These data do not show causal relationship between quetiapine treatment and death in elderly patients with dementia.

Hepatic effects
If jaundice develops, Quetiapine film-coated tablets should be discontinued.

Concomitant illness
Dysphagia (see Section 4.8 Undesirable effects) and aspiration have been reported with Quetiapine. Although a causal relationship with aspiration pneumonia has not been established, Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures undertaken.

Lactose
Quetiapine Film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.
Additional information
Quetiapine data in combination with divalproex (valproate semisodium) or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 Undesirable effects and 5.1 Pharmacodynamic properties). The data showed an additive effect at week 3.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Given the primary central nervous system effects of quetiapine, it should be used with caution in combination with other centrally acting drugs and alcohol.

Cytochrome P450 (CYP) 3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine and a CYP3A4 inhibitor is contraindicated. It is also not recommended to take quetiapine together with grapefruit juice.

Quetiapine did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. However, in a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur which can influence the effect of quetiapine therapy. Co-administration of quetiapine and phenytoin (microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approximately 450%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine therapy should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer treatment is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate) (see also section 4.4 Special warnings and special precautions for use).

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 inhibitor).

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However co-administration of quetiapine and thioridazine caused increases in the clearance of quetiapine of about 70%.

The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine, a known P450 enzyme inhibitor.

The pharmacokinetics of lithium were not altered when co-administered with quetiapine.

The pharmacokinetics of valproic acid and quetiapine were not altered to a clinically relevant extent when co-administered as valproate semisodium (also known as divalproex sodium (USAN)) and Quetiapine film-coated tablets (quetiapine fumarate). Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.

Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QTc interval.

4.6 PREGNANCY AND LACTATION
The safety and efficacy of quetiapine during human pregnancy have not yet been established. Up to now there are no indications for harmfulness in animal tests, possible effects on the foetal eye have not been examined though. Therefore, Quetiapine should only be used during pregnancy if the benefits justify the potential risks. Following pregnancies in which Quetiapine was used, neonatal withdrawal symptoms were observed.
The degree to which quetiapine is excreted into human milk is unknown. Women who are breast feeding should therefore be advised to avoid breast feeding while taking Quetiapine Film-coated Tablets.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness and may cause somnolence. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility to this is known.

4.8 UNDESIRABLE EFFECTS
The most commonly reported Adverse Drug Reactions (ADRs) with Quetiapine Film-coated Tablets are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension, and dyspepsia.

As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with Quetiapine Film-coated Tablets.

The incidences of ADRs associated with quetiapine therapy, are tabulated below according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

**Blood and lymphatic system disorders**
- **Common:** Leucopenia
- **Uncommon:** Eosinophilia, Thrombocytopenia
- **Unknown:** Neutropenia

**Immune system disorders**
- **Uncommon:** Hypersensitivity
- **Very rare:** Anaphylactic reaction

**Endocrine disorders**
- **Common:** Hyperprolactinaemia

**Metabolism and nutritional disorders**
- **Common:** Increased appetite
- **Very rare:** Diabetes Mellitus

**Psychiatric disorders**
- **Common:** Abnormal dreams and nightmares

**Nervous system disorders**
- **Very Common:** Dizziness, somnolence, headache
- **Common:** Syncope, Extrapyramidal symptoms, Dysarthria
- **Uncommon:** Seizure, Restless leg syndrome, Tardive dyskinesia

**Cardiac disorders**
- **Common:** Tachycardia
Eye disorders
Common: Vision blurred

Vascular disorders
Common: Orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Common: Rhinitis

Gastrointestinal disorders
Very Common: Dry mouth
Common: Constipation, dyspepsia
Uncommon: Dysphagia

Hepato-biliary disorders
Rare: Jaundice
Very rare: Hepatitis

Skin and subcutaneous tissue disorders
Very rare: Angioedema, Stevens-Johnson syndrome

Reproductive system and breast disorders
Rare: Priapism, galactorrhoea

General disorders and administration site conditions
Very Common: Withdrawal (discontinuation) symptoms
Common: Mild asthenia, peripheral oedema, irritability
Rare: Neuroleptic malignant syndrome

Investigations
Very Common: Elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain
Common: Elevations in serum transaminases (ALT, AST), decreased neutrophil count, blood glucose increased to hyperglycaemic levels
Uncommon: Elevations in gamma-GT levels, platelet count decreased
Rare: Elevations in blood creatine phosphokinase, Venous thromboembolism

(1) See section 4.4 Special Warnings and Special Precautions for Use.

(2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of SEROQUEL.

(3) Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT levels have been observed in some patients administered SEROQUEL.

(4) As with other antipsychotics with alpha, adrenergic blocking activity, SEROQUEL may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some
patients, syncope, especially during the initial dose-titration period. (See section 4.4 Special warnings and special precautions for use).

(5) Exacerbation of pre-existing diabetes has been reported in very rare cases.

(6) Calculation of frequency for these ADRs have been taken from post-marketing data only.

(7) Fasting blood glucose ≥7.0 mmol/L or a non fasting blood glucose ≥11.1 mmol/L on at least one occasion.

(8) An increase in the rate of dysphagia with SEROQUEL vs. placebo was only observed in the clinical trials in bipolar depression.

(9) Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.

(10) The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.

(11) Triglycerides ≥200 mg/dL (≥2.258 mmol/L) (patients ≥18 years of age) or ≥150 mg/dL (≥1.694 mmol/L) (patients <18 years of age) on at least one occasion.

(12) Cholesterol ≥240 mg/dL (≥6.2064 mmol/L) (patients ≥18 years of age) or ≥200 mg/dL (≥5.172 mmol/L) (patients <18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥30 mg/dL (≥0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥1.07 mmol/L).

(13) See text below.

(14) Platelets ≥100 x 10^9/L on at least one occasion.

(15) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.

(16) Prolactin levels (patients>18 years of age):>20 μg/L (>869.56 pmol/L) males;>30 μg/L (>1304.34 pmol/L) females at any time.

(17) May lead to falls.

(18) HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported with the use of neuroleptics and are considered class effects (see Section 4.4 Special warnings and special precautions for use).

In short-term, placebo-controlled clinical trials in bipolar depression the aggregated incidence of extrapyramidal symptoms was 8.9% for Quetiapine compared to 3.8% for placebo, though the incidence of the individual adverse events were generally low and did not exceed 4% in any treatment group. In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for Quetiapine and 8.0% for placebo; bipolar mania: 11.2% for Quetiapine and 11.4% for placebo).

Quetiapine treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T4 and free T4. The reduction in total and free T4 was maximal within the first two to four weeks of quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. Smaller decreases in total T3 and reverse T3 were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal
increases in TSH were not observed, with no indication that quetiapine causes clinically relevant hypothyroidism.

4.9 OVERDOSE
Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of quetiapine alone. However, survival has also been reported following acute overdoses of up to 30 grams.

In post-marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma or QT-prolongation.

In general, reported signs and symptoms were those resulting from an exaggeration of the known pharmacological effects of the active substance, i.e. drowsiness and sedation, tachycardia and hypotension.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See section 4.4 : Special warnings and special precautions for use: Cardiovascular).

Management
There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal should be considered.

Close medical supervision and monitoring should be continued until the patient recovers.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic Group: Antipsychotics
Therapeutic classification: N05AH04

Mechanism of action
Quetiapine is an atypical antipsychotic agent. Quetiapine and the active metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit an affinity for brain serotonin (5HT₂) and dopamine D₁ and D₂ receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT₂ relative to D₂ receptors which is believed to contribute to the antipsychotic properties and low extrapyramidal symptoms (EPS) liability of quetiapine compared to typical antipsychotics. Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic α₁ receptors, with a lower affinity for adrenergic α₂-receptors and serotonin 5HT₁A receptors.
Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

Pharmacodynamic effect
Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D₂-receptor blockade. In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D₂ receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D₂ receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration. The extent to which the norquetiapine metabolite contributes to the pharmacological activity of Quetiapine in humans is not known.
Clinical Efficacy

The results of three placebo-controlled clinical trials in patients with schizophrenia, including one that used a dose range of Quetiapine of 75 to 750 mg/day, identified no difference between Quetiapine and placebo in the incidence of EPS or use of concomitant anticholinergics. In four controlled trials, evaluating doses of Quetiapine up to 800 mg for the treatment of bipolar mania, two each in monotherapy and as adjunct therapy to lithium or valproate semisodium, there were no differences between the Quetiapine and placebo treatment groups in the incidence of EPS or concomitant use of anticholinergics.

In clinical trials, Quetiapine has been shown to be effective in the treatment of both positive and negative symptoms of schizophrenia. In one trial against chlorpromazine, and two against haloperidol, Quetiapine showed similar short-term efficacy.

In clinical trials, Quetiapine has been shown to be effective as monotherapy or as adjunct therapy in reducing manic symptoms in patients with bipolar mania. The mean last week median dose of Quetiapine in responders, was approximately 600 mg and approximately 85% of the responders were in the dose range of 400 to 800 mg per day.

In 4 clinical trials in patients with depressive episodes in bipolar I or bipolar II disorder, with and without rapid cycling courses, 51% of quetiapine treated patients had at least a 50% improvement in MADRS total score at week 8 compared to 37% of the placebo treated patients. The anti-depressant effect was significant at Day 8 (week 1). There were fewer episodes of treatment-emergent mania with Quetiapine than with placebo. In continuation treatment the anti-depressant effect was maintained for patients on Quetiapine (mean duration of treatment 30 weeks). Quetiapine reduced the risk of a recurrent mood (manic and depressed) event by 49%. Quetiapine was superior to placebo in treating the anxiety symptoms associated with bipolar depression as assessed by mean change from baseline to week 8 in HAM-A total score.

In one long-term study (up to 2 years treatment, mean quetiapine exposure 191 days) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed), in patients with bipolar I disorder. The number of patients with a mood event was 91 (22.5%) in the quetiapine group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups respectively. In patients who responded to quetiapine, when comparing continued treatment with quetiapine to switching to lithium, the results indicated that a switch to lithium treatment does not appear to be associated with an increased time to recurrence of a mood event. In two recurrence prevention studies evaluating Quetiapine in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with Quetiapine was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). The risk of a recurrent event was reduced by 70%. Quetiapine was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In placebo-controlled monotherapy trials in patients with a baseline neutrophil count ≥1.5 X 10^9/L, the incidence of at least one occurrence of neutrophil count <1.5 X 10^9/L, was 1.72% in patients treated with Quetiapine compared to 0.73% in placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator; patients with a baseline neutrophil count ≥1.5 X 10^9/L), the incidence of at least one occurrence of neutrophil count <0.5 X 10^9/L was 0.21% in patients treated with Quetiapine and 0% in placebo treated patients and the incidence ≥0.5 - <1.0 X 10^9/L was 0.75% in patients treated with Quetiapine and 0.11% in placebo-treated patients.

Children and adolescents (10 to 17 years of age)

The efficacy and safety of Quetiapine was studied in a 3-week placebo controlled study for the treatment of mania (n= 284 patients from the US, aged 10-17). About 45% of the patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo controlled study for the treatment of schizophrenia (n = 222 patients, aged 13-17) was performed. In both studies, patients with known lack of response to Quetiapine were excluded. Treatment with Quetiapine was initiated at 50 mg/day and on day 2 increased to 100 mg/day; subsequently the dose was titrated to a target dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day) using increments of 100 mg/day given two or three times daily.
In the mania study, the difference in LS mean change from baseline in YMRS total score (active minus placebo) was −5.21 for Quetiapine 400 mg/day and −6.56 for Quetiapine 600 mg/day. Responder rates (YMRS improvement ≥ 50%) were 64% for Quetiapine 400 mg/day, 58% for 600 mg/day and 37% in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score (active minus placebo) was −8.16 for Quetiapine 400 mg/day and −9.29 for Quetiapine 800 mg/day. Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine was superior to placebo with respect to the percentage of patients achieving response, defined as ≥ 30% reduction from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

No data are available on maintenance of effect or recurrence prevention in this age group. A 26-week open-label extension to the acute trials (n= 380 patients), with Quetiapine flexibly dosed at 400-800 mg/day, provided additional safety data. Increases in blood pressure were reported in children and adolescents and increased appetite, extrapyramidal symptoms and elevations in serum prolactin were reported with higher frequency in children and adolescents than in adult patients (see Section 4.4 Special warnings and special precautions for use and Section 4.8 Undesirable effects).

Extrapyramidal Symptoms
In a short-term placebo-controlled monotherapy trial in adolescent patients (13-17 years of age) with schizophrenia, the aggregated incidence of extrapyramidal symptoms was 12.9% for quetiapine and 5.3% for placebo, though the incidence of the individual adverse events (e.g. akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar mania, the aggregated incidence of extrapyramidal symptoms was 3.6% for quetiapine and 1.1% for placebo. In a long-term open label study of schizophrenia and bipolar mania, the aggregated incidence of treatment-emergent EPS was 10%.

Weight Gain
In short-term clinical trials in paediatric patients (10-17 years of age), 17% of quetiapine-treated patients and 2.5% of placebo-treated patients gained ≥ 7% of their body weight. When adjusting for normal growth over longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who were treated with quetiapine for at least 26 weeks met this criterion.

Suicide/Suicidal thoughts or Clinical worsening
In short-term placebo-controlled clinical trials in paediatric patients with schizophrenia, the incidence of suicide related events was 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients <18 years of age. In short-term placebo-controlled trials in paediatric patients with bipolar mania, the incidence of suicide related events was 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients <18 years of age.

5.2 PHARMACOKINETIC PROPERTIES
Quetiapine is well absorbed and extensively metabolised following oral administration. The bioavailability of quetiapine is not significantly affected by administration with food. Quetiapine is approximately 83% bound to plasma proteins. Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine. The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively.

Clinical trials have demonstrated that Quetiapine is effective when given twice a day. This is further supported by data from a positron emission tomography (PET) study which identified that 5HT2 and D2 receptor occupancy are maintained for up to 12 hours after dosing with quetiapine. The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range. The kinetics of quetiapine do not differ between men and women. The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73m²), but the individual clearance
values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Quetiapine is extensively metabolised, with parent compound accounting for less than 5% of unchanged drug – related material in the urine or faeces, following the administration of radiolabelled quetiapine. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces. The mean quetiapine plasma clearance decreases by approx. 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see section 4.2 Posology and method of administration).

In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

In a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of quetiapine given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean C\text{max} and AUC of quetiapine of 235% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%. The mean half-life of quetiapine increased from 2.6 to 6.8 hours, but the mean t\text{max} was unchanged.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Children and adolescents (10 to 17 years of age)
Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though C\text{max} in children was at the higher end of the range observed in adults. The AUC and C\text{max} for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

5.3 PRECLINICAL SAFETY DATA
There was no evidence of genotoxicity in a series of in vitro and in vivo genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in long-term clinical research:

In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy, a lowering in plasma T3 levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts.

Taking these findings into consideration, the benefits of the treatment with quetiapine need to be balanced against the safety risks for the patient.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Core
Microcrystalline cellulose
Povidone K29-32
Calcium hydrogen phosphate dihydrate
Sodium starch glycolate (Type A)
Lactose monohydrate
Magnesium stearate
Film-coat
Opadry II White 33G28435 containing:
Hypermellose 6cP
Titanium dioxide
Lactose monohydrate
Macrogol 3350
Triacetin

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions

6.5 NATURE AND CONTENTS OF CONTAINER
Blisters (PVC/PVDC/Al and PVC/Al) Pack sizes: 6, 10, 20, 30, 50, 60, 90, 100 tablets*
Plastic (polyethylene) tablet containers Pack sizes: 6, 10, 20, 30, 50, 60, 90, 100 tablets*
* Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0166

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/02/2011

10 DATE OF REVISION OF THE TEXT
25/02/2011
1 NAME OF THE MEDICINAL PRODUCT
Quetiapine 300mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 300mg quetiapine (as fumarate).

Excipients:
Each tablet contains 62.10 mg lactose monohydrate
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
White, 19 x 7.6 mm, oval, biconvex, engraved with Q on one side and with 300 on the other side.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Quetiapine is indicated for the treatment of:
Schizophrenia.

Bipolar disorder including:
- manic episodes associated with bipolar disorder
- major depressive episodes in bipolar disorder
- preventing recurrence in bipolar disorder in patients whose manic, mixed or depressive episode has responded to quetiapine treatment.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Quetiapine Film-coated Tablets can be administered with or without food.

Adults
For the treatment of schizophrenia: Quetiapine should be administered twice a day. The total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4).

From Day 4 onwards, the dose should be titrated to the usual effective dose range of 300 to 450 mg/day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 to 750 mg/day.

For the treatment of manic episodes associated with bipolar disorder: Quetiapine should be administered twice a day. As monotherapy or as adjunct to mood stabilisers, the total daily dose for the first four days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg per day by Day 6 should be in increments of no greater than 200 mg per day.

The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg per day. The usual effective dose is in the range of 400 to 800 mg per day.

For the treatment of depressive episodes in bipolar disorder: Quetiapine should be administered once daily at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group. Individual patients may benefit from a 600 mg dose. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered. When treating depressive episodes in bipolar disorder, treatment should be initiated by physicians experienced in treating bipolar disorder.

For preventing recurrence in bipolar disorder: For prevention of recurrence of manic, depressive and mixed episodes in bipolar disorder, patients who have responded to quetiapine for acute treatment of bipolar disorder should continue therapy at the same dose. The dose may then be adjusted depending on clinical response and tolerability of the individual patient, within the range of 300 to 800 mg/day administered twice daily. It is important that the lowest effective dose is used for maintenance therapy.
Elderly
As with other antipsychotics, Quetiapine Film-coated Tablets should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on Quetiapine Film-coated tablets 25 mg/day. The dose should be increased daily in increments of 25 to 50 mg, to an effective dose, which is likely to be lower than that in younger patients.

Efficacy and safety have not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Children and adolescents
Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in sections 4.4, 4.8, 5.1 and 5.2.

Renal impairment
Dose adjustment is not necessary in patients with renal impairment.

Hepatic impairment
Quetiapine is extensively metabolised by the liver. Therefore, quetiapine should be used with caution in patients with known hepatic impairment, especially during the initial dose titration period. Patients with known hepatic impairment should be started with 25 mg/day. The dosage should be increased daily with increments of 25 - 50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.

4.3 CONTRAINDICATIONS
Quetiapine film-coated tablets are contraindicated in patients who are hypersensitive to any component of this product.

Concomitant administration of cytochrome P450 3A4 inhibitors such as HIV protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated. (See also section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Children and adolescents (10 to 17 years of age)
Quetiapine Film-coated tablets are not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials have shown that in addition to the known safety profile identified in adults (see section 4.8 Undesirable effects), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, and extrapyramidal symptoms) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

Furthermore, the long-term safety implications of treatment on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

In placebo-controlled clinical trials with children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia and bipolar mania (see section 4.8 Undesirable effects).

Suicide/suicidal thoughts or clinical worsening
Depression in bipolar disorder is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

In clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients less than 25 years of age who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively).
**Somnolence**
Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see Section 4.8 Undesirable effects). In clinical trials for treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

**Cardiovascular disease**
Quetiapine Film-coated Tablets should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.

Quetiapine may induce orthostatic hypotension, especially during the initial dose-titration period; this is more common in elderly patients than in younger patients. Dose reduction or more gradual titration should be considered if this occurs.

**Seizures**
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with Quetiapine or placebo. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see section 4.8 Undesirable effects).

**Extrapyramidal symptoms**
In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder (see Section 4.8 Undesirable effects).

**Tardive dyskinesia**
Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic drugs including quetiapine. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of Quetiapine Film-coated Tablets should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see section 4.8 Undesirable effects).

**Neuroleptic malignant syndrome**
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including Quetiapine Film-coated Tablets (see Section 4.8 Undesirable effects). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, Quetiapine Film-coated Tablets should be discontinued and appropriate medical treatment given.

**Severe neutropenia**
Severe neutropenia (neutrophil count < 0.5 X 10^9/L) has been uncommonly reported in quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with Quetiapine. There was no apparent dose relationship. During post-marketing experience, resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. Quetiapine should be discontinued in patients with a neutrophil count < 1.0 X 10^9/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X 10^9/L). (See section 5.1 Pharmacodynamic properties).

**Interactions**
See also Section 4.5 Interactions with other medicinal products and other forms of interaction.

Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer treatment. It is important that any change in the inducer treatment is gradual, and if required, inducer may be replaced with a non-inducer (e.g. sodium valproate).
Hyperglycaemia
Hyperglycaemia or exacerbation of pre-existing diabetes has been reported during treatment with quetiapine. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus (see also section 4.8 Undesirable effects).

Lipids
Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8 Undesirable effects). Lipid changes should be managed as clinically appropriate.

QT prolongation
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT interval. However, with overdose (see section 4.9) QT prolongation was observed. As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when quetiapine is prescribed with medicines known to increase QTc interval, and concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Acute withdrawal reactions
Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability have been described after abrupt cessation of quetiapine. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Gradual withdrawal over a period of at least one to two weeks is advisable (see Section 4.8 Undesirable effects).

Elderly with dementia-related psychosis
Quetiapine is not approved for the treatment of patients with dementia-related psychosis.

An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomized placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with an increased risk of stroke.

In a meta-analysis of atypical antipsychotic drugs, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. However in two 10-week placebo-controlled quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% compared to 3.2% in the placebo group. The patients in these trials died of a variety of causes that were consistent with expectations for this population. These data do not show causal relationship between quetiapine treatment and death in elderly patients with dementia.

Hepatic effects
If jaundice develops, Quetiapine film-coated tablets should be discontinued.

Concomitant illness
Dysphagia (see Section 4.8 Undesirable effects) and aspiration have been reported with Quetiapine. Although a causal relationship with aspiration pneumonia has not been established, Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures undertaken.

Lactose
Quetiapine Film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.
Additional information
Quetiapine data in combination with divalproex (valproate semisodium) or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 Undesirable effects and 5.1 Pharmacodynamic properties). The data showed an additive effect at week 3.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Given the primary central nervous system effects of quetiapine, it should be used with caution in combination with other centrally acting drugs and alcohol.

Cytochrome P450 (CYP) 3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine and a CYP3A4 inhibitor is contraindicated. It is also not recommended to take quetiapine together with grapefruit juice.

Quetiapine did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. However, in a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur which can influence the effect of quetiapine therapy. Co-administration of quetiapine and phenytoin (microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approximately 450%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine therapy should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer treatment is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate) (see also section 4.4 Special warnings and special precautions for use).

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 inhibitor).

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However co-administration of quetiapine and thioridazine caused increases in the clearance of quetiapine of about 70%.

The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine, a known P450 enzyme inhibitor.

The pharmacokinetics of lithium were not altered when co-administered with quetiapine.

The pharmacokinetics of valproic acid and quetiapine were not altered to a clinically relevant extent when co-administered as valproate semisodium (also known as divalproex sodium (USAN)) and Quetiapine film-coated tablets (quetiapine fumarate). Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.

Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QTc interval.

4.6 PREGNANCY AND LACTATION
The safety and efficacy of quetiapine during human pregnancy have not yet been established. Up to now there are no indications for harmfulness in animal tests, possible effects on the foetal eye have not been examined though. Therefore, Quetiapine should only be used during pregnancy if the benefits justify the potential risks. Following pregnancies in which Quetiapine was used, neonatal withdrawal symptoms were observed.
The degree to which quetiapine is excreted into human milk is unknown. Women who are breast feeding should therefore be advised to avoid breast feeding while taking Quetiapine Film-coated Tablets.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness and may cause somnolence. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility to this is known.

4.8 UNDESIRABLE EFFECTS
The most commonly reported Adverse Drug Reactions (ADRs) with Quetiapine Film-coated Tablets are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension, and dyspepsia.

As with other antipsychotics, weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with Quetiapine Film-coated Tablets.

The incidences of ADRs associated with quetiapine therapy, are tabulated below according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

**Blood and lymphatic system disorders**
- **Common:** Leucopenia
- **Unknown:** Neutropenia

**Immune system disorders**
- **Uncommon:** Hypersensitivity

**Endocrine disorders**
- **Common:** Hyperprolactinaemia

**Metabolism and nutritional disorders**
- **Common:** Increased appetite

**Psychiatric disorders**
- **Common:** Abnormal dreams and nightmares

**Nervous system disorders**
- **Very Common:** Dizziness, somnolence, headache
- **Common:** Syncope, Extrapyramidal symptoms, Dysarthria
- **Uncommon:** Seizure, Restless leg syndrome, Tardive dyskinesia

**Cardiac disorders**
- **Common:** Tachycardia
Eye disorders
Common: Vision blurred
Vascular disorders
Common: Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders
Common: Rhinitis
Gastrointestinal disorders
Very Common: Dry mouth
Common: Constipation, dyspepsia
Uncommon: Dysphagia
Hepato-biliary disorders
Rare: Jaundice
Very rare: Hepatitis
Skin and subcutaneous tissue disorders
Very rare: Angioedema, Stevens-Johnson syndrome
Reproductive system and breast disorders
Rare: Priapism, galactorrhoea
General disorders and administration site conditions
Very Common: Withdrawal (discontinuation) symptoms
Common: Mild asthenia, peripheral oedema, irritability
Rare: Neuroleptic malignant syndrome
Investigations
Very Common: Elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain
Common: Elevations in serum transaminases (ALT, AST), decreased neutrophil count, blood glucose increased to hyperglycaemic levels
Uncommon: Elevations in gamma-GT levels, platelet count decreased
Rare: Elevations in blood creatine phosphokinase, Venous thromboembolism

(1) See section 4.4 Special Warnings and Special Precautions for Use.

(2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of SEROQUEL.

(3) Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT levels have been observed in some patients administered SEROQUEL.

(4) As with other antipsychotics with alpha, adrenergic blocking activity, SEROQUEL may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some...
patients, syncope, especially during the initial dose-titration period. (See section 4.4 Special warnings and special precautions for use).

(5) Exacerbation of pre-existing diabetes has been reported in very rare cases.

(6) Calculation of frequency for these ADRs have been taken from post-marketing data only.

(7) Fasting blood glucose ≥7.0 mmol/L or a non fasting blood glucose ≥11.1 mmol/L on at least one occasion.

(8) An increase in the rate of dysphagia with SEROQUEL vs. placebo was only observed in the clinical trials in bipolar depression.

(9) Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.

(10) The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.

(11) Triglycerides ≥200 mg/dL (≥2.258 mmol/L) (patients ≥18 years of age) or ≥150 mg/dL (≥1.694 mmol/L) (patients <18 years of age) on at least one occasion.

(12) Cholesterol ≥240 mg/dL (≥6.2064 mmol/L) (patients ≥18 years of age) or ≥200 mg/dL (≥5.172 mmol/L) (patients <18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥30 mg/dL (≥0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥1.07 mmol/L).

(13) See text below.

(14) Platelets ≥100 x 10^9/L on at least one occasion.

(15) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.

(16) Prolactin levels (patients >18 years of age): >20 μg/L (>869.56 pmol/L) males; >30 μg/L (>1304.34 pmol/L) females at any time.

(17) May lead to falls.

(18) HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported with the use of neuroleptics and are considered class effects (see Section 4.4 Special warnings and special precautions for use).

In short-term, placebo-controlled clinical trials in bipolar depression the aggregated incidence of extrapyramidal symptoms was 8.9% for Quetiapine compared to 3.8% for placebo, though the incidence of the individual adverse events were generally low and did not exceed 4% in any treatment group. In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for Quetiapine and 8.0% for placebo; bipolar mania: 11.2% for Quetiapine and 11.4% for placebo).

Quetiapine treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T₄ and free T₄. The reduction in total and free T₄ was maximal within the first two to four weeks of quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T₄, irrespective of the duration of treatment. Smaller decreases in total T₃ and reverse T₃ were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal
increases in TSH were not observed, with no indication that quetiapine causes clinically relevant hypothyroidism.

**Children and adolescents (10 to 17 years of age)**
The same ADRs described above for adults should be considered for children and adolescents. The following table summarises ADRs that occur in a higher frequency category in children and adolescent patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

**Metabolism and nutritional disorders**
*Very common:* Increased appetite

**Investigations**
*Very common:* Elevations in prolactin $^1$, increases in blood pressure $^2$

**Nervous system disorders**
*Very common:* Extrapyramidal symptoms $^3$

**General disorders and administration site conditions**
*Common:* Irritability $^4$

(1) Prolactin levels (patients < 18 years of age): $>20 \mu g/L$ ($>869.56$ pmol/L) males; $>26 \mu g/L$ ($>1130.428$ pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level $>100 \mu g/L$.

(2) Based on shifts above clinically significant thresholds (adapted from the National Institute of Health criteria) or increases $>20$ mmHg for systolic or $>10$ mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.

(3) See Section 5.1 Pharmacodynamic properties.

(4) Note: The frequency is consistent to that observed in adults, but irritability might be associated with different clinical implications in children and adolescents as compared to adults.

### 4.9 OVERDOSE
Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of quetiapine alone. However, survival has also been reported following acute overdoses of up to 30 grams.

In post-marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma or QT-prolongation.

In general, reported signs and symptoms were those resulting from an exaggeration of the known pharmacological effects of the active substance, i.e. drowsiness and sedation, tachycardia and hypotension.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See section 4.4: Special warnings and special precautions for use: Cardiovascular).

**Management**
There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal should be considered.

Close medical supervision and monitoring should be continued until the patient recovers.
5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic Group: Antipsychotics
Therapeutic classification: N05AH04

Mechanism of action
Quetiapine is an atypical antipsychotic agent. Quetiapine and the active metabolite, norquetiapine, interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit an affinity for brain serotonin (5HT2) and dopamine D1 and D2 receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT2 relative to D2 receptors which is believed to contribute to the antipsychotic properties and low extrapyramidal symptoms (EPS) liability of quetiapine compared to typical antipsychotics. Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity for adrenergic α2-receptors and serotonin 5HT1A receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

Pharmacodynamic effect
Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D2-receptor blockade. In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D2 receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D2 receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration. The extent to which the norquetiapine metabolite contributes to the pharmacological activity of Quetiapine in humans is not known.

Clinical Efficacy
The results of three placebo-controlled clinical trials in patients with schizophrenia, including one that used a dose range of Quetiapine of 75 to 750 mg/day, identified no difference between Quetiapine and placebo in the incidence of EPS or use of concomitant anticholinergics. In four controlled trials, evaluating doses of Quetiapine up to 800 mg for the treatment of bipolar mania, two each in monotherapy and as adjunct therapy to lithium or valproate semisodium, there were no differences between the Quetiapine and placebo treatment groups in the incidence of EPS or concomitant use of anticholinergics.

In clinical trials, Quetiapine has been shown to be effective in the treatment of both positive and negative symptoms of schizophrenia. In one trial against chlorpromazine, and two against haloperidol, Quetiapine showed similar short-term efficacy.

In clinical trials, Quetiapine has been shown to be effective as monotherapy or as adjunct therapy in reducing manic symptoms in patients with bipolar mania. The mean last week median dose of Quetiapine in responders, was approximately 600 mg and approximately 85% of the responders were in the dose range of 400 to 800 mg per day.

In 4 clinical trials in patients with depressive episodes in bipolar I or bipolar II disorder, with and without rapid cycling courses, 51% of quetiapine treated patients had at least a 50% improvement in MADRS total score at week 8 compared to 37% of the placebo treated patients. The anti-depressant effect was significant at Day 8 (week 1). There were fewer episodes of treatment-emergent mania with Quetiapine than with placebo. In continuation treatment the anti-depressant effect was maintained for patients on Quetiapine (mean duration of treatment 30 weeks). Quetiapine reduced the risk of a recurrent mood (manic and depressed) event by 49%. Quetiapine was superior to placebo in treating the anxiety symptoms associated with bipolar depression as assessed by mean change from baseline to week 8 in HAM-A total score.

In one long-term study (up to 2 years treatment, mean quetiapine exposure 191 days) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or
depressed), in patients with bipolar I disorder. The number of patients with a mood event was 91 (22.5%) in the quetiapine group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups respectively. In patients who responded to quetiapine, when comparing continued treatment with quetiapine to switching to lithium, the results indicated that a switch to lithium treatment does not appear to be associated with an increased time to recurrence of a mood event. In two recurrence prevention studies evaluating Quetiapine in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with Quetiapine was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). The risk of a recurrent event was reduced by 70%. Quetiapine was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In placebo-controlled monotherapy trials in patients with a baseline neutrophil count $\geq 1.5 \times 10^9$/L, the incidence of at least one occurrence of neutrophil count $<1.5 \times 10^9$/L, was 1.72% in patients treated with Quetiapine compared to 0.73% in placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator; patients with a baseline neutrophil count $\geq 1.5 \times 10^9$/L), the incidence of at least one occurrence of neutrophil count $<0.5 \times 10^9$/L was 0.21% in patients treated with Quetiapine and 0% in placebo treated patients and the incidence $\geq 0.5 - <1.0 \times 10^9$/L was 0.75% in patients treated with Quetiapine and 0.11% in placebo-treated patients.

**Children and adolescents (10 to 17 years of age)**

The efficacy and safety of Quetiapine was studied in a 3-week placebo controlled study for the treatment of mania (n= 284 patients from the US, aged 10-17). About 45% of the patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo controlled study for the treatment of schizophrenia (n = 222 patients, aged 13-17) was performed. In both studies, patients with known lack of response to Quetiapine were excluded. Treatment with Quetiapine was initiated at 50 mg/day and on day 2 increased to 100 mg/day; subsequently the dose was titrated to a target dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day) using increments of 100 mg/day given two or three times daily.

In the mania study, the difference in LS mean change from baseline in YMRS total score (active minus placebo) was –5.21 for Quetiapine 400 mg/day and –6.56 for Quetiapine 600 mg/day. Responder rates (YMRS improvement $\geq 50\%$) were 64% for Quetiapine 400 mg/day, 58% for 600 mg/day and 37% in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score (active minus placebo) was –8.16 for Quetiapine 400 mg/day and –9.29 for Quetiapine 800 mg/day. Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine was superior to placebo with respect to the percentage of patients achieving response, defined as $\geq 30\%$ reduction from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

No data are available on maintenance of effect or recurrence prevention in this age group. A 26-week open-label extension to the acute trials (n= 380 patients), with Quetiapine flexibly dosed at 400-800 mg/day, provided additional safety data. Increases in blood pressure were reported in children and adolescents and increased appetite, extrapyramidal symptoms and elevations in serum prolactin were reported with higher frequency in children and adolescents than in adult patients (see Section 4.4 Special warnings and special precautions for use and Section 4.8 Undesirable effects).

**Extrapyramidal Symptoms**

In a short-term placebo-controlled monotherapy trial in adolescent patients (13-17 years of age) with schizophrenia, the aggregated incidence of extrapyramidal symptoms was 12.9% for quetiapine and 5.3% for placebo, though the incidence of the individual adverse events (e.g. akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar mania, the aggregated incidence of extrapyramidal symptoms was 3.6% for quetiapine and 1.1% for placebo. In a long-term open label study of schizophrenia and bipolar mania, the aggregated incidence of treatment-emergent EPS was 10%.
Weight Gain
In short-term clinical trials in paediatric patients (10-17 years of age), 17% of quetiapine-treated patients and 2.5% of placebo-treated patients gained ≥7% of their body weight. When adjusting for normal growth over longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who were treated with quetiapine for at least 26 weeks met this criterion.

Suicide/Suicidal thoughts or Clinical worsening
In short-term placebo-controlled clinical trials in paediatric patients with schizophrenia, the incidence of suicide related events was 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients <18 years of age. In short-term placebo-controlled trials in paediatric patients with bipolar mania, the incidence of suicide related events was 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients <18 years of age.

5.2 PHARMACOKINETIC PROPERTIES
Quetiapine is well absorbed and extensively metabolised following oral administration. The bioavailability of quetiapine is not significantly affected by administration with food. Quetiapine is approximately 83% bound to plasma proteins. Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine. The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively.

Clinical trials have demonstrated that Quetiapine is effective when given twice a day. This is further supported by data from a positron emission tomography (PET) study which identified that 5HT2 and D2 receptor occupancy are maintained for up to 12 hours after dosing with quetiapine. The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range. The kinetics of quetiapine do not differ between men and women. The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73m²), but the individual clearance values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Quetiapine is extensively metabolised, with parent compound accounting for less than 5% of unchanged drug related material in the urine or faeces, following the administration of radiolabelled quetiapine. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces. The mean quetiapine plasma clearance decreases by approx. 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see section 4.2 Posology and method of administration).

In vivo investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

In a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of quetiapine given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean Cmax and AUC of quetiapine of 235% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%. The mean half-life of quetiapine increased from 2.6 to 6.8 hours, but the mean tmax was unchanged.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.
Children and adolescents (10 to 17 years of age)
Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though \( C_{\text{max}} \) in children was at the higher end of the range observed in adults. The AUC and \( C_{\text{max}} \) for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

5.3 PRECLINICAL SAFETY DATA
There was no evidence of genotoxicity in a series of in vitro and in vivo genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in long-term clinical research:

In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy, a lowering in plasma T3 levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts.

Taking these findings into consideration, the benefits of the treatment with quetiapine need to be balanced against the safety risks for the patient.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Core
- Microcrystalline cellulose
- Povidone K29-32
- Calcium hydrogen phosphate dihydrate
- Sodium starch glycolate (Type A)
- Lactose monohydrate
- Magnesium stearate

Film-coat
- Opadry II White 33G28435 containing:
  - Hypromellose 6cP
  - Titanium dioxide
  - Lactose monohydrate
  - Macrogol 3350
  - Triacetin

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions

6.5 NATURE AND CONTENTS OF CONTAINER
Blisters (PVC/PVDC/Al and PVC/Al) Pack sizes: 6, 10, 20, 30, 50, 60, 90, 100 tablets*
Plastic (polyethylene) tablet containers Pack sizes: 6, 10, 20, 30, 50, 60, 90, 100 tablets*
* Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0167

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/02/2011

10 DATE OF REVISION OF THE TEXT
25/02/2011
The Patient Information Leaflet (PIL) below is the leaflet text agreed at the end of the procedure. The marketing authorisation holder has committed to submit the mock-up of the PIL for review to the regulatory authority before marketing the product.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Quetiapine 25 mg Film-coated Tablets
Quetiapine 100 mg Film-coated Tablets
Quetiapine 150 mg Film-coated Tablets
Quetiapine 200 mg Film-coated Tablets
Quetiapine 300 mg Film-coated Tablets

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Quetiapine Film-coated Tablets are and what they are used for
2. Before you take Quetiapine Film-coated Tablets
3. How to take Quetiapine Film-coated Tablets
4. Possible side effects
5. How to store Quetiapine Film-coated Tablets
6. Further information

1. WHAT QUETIAPINE FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

Quetiapine Film-coated tablets contain a medicine called quetiapine. This belongs to a group of medicines called antipsychotics. These medicines help with the effects of some types of mental illness such as:
- Hallucinations (like hearing unexplained voices), strange and frightening thoughts, changes in how you act, and feeling alone and confused. This is also known as schizophrenia.
- Effects on your mood and feeling very ‘high’ or excited. You may find that you need to sleep less than usual. You may also be more talkative and have racing thoughts or ideas. You may also feel more irritable than usual. This is also known as bipolar mania.
- Effects on your mood whereby you feel sad all the time. You may find that you feel depressed, feel guilty, lack energy, lose your appetite and/or can’t sleep. This is also known as bipolar depression.

Your doctor may continue to give you Quetiapine when you are feeling better to prevent your symptoms from returning.

You may find it helpful to tell a friend or relative that you are suffering from these symptoms, and ask them to read this leaflet. You might ask them to tell you if they think your symptoms are getting worse, or if they are worried about any other changes in your behaviour.

2. BEFORE YOU TAKE QUETIAPINE FILM-COATED TABLETS

Do not take Quetiapine if:
- you are allergic (hypersensitive) to quetiapine or any of the other ingredients of Quetiapine Film-coated tablets (see Section 6: Further Information).
- you are taking any of the following medicines:
  - protease inhibitors, such as nelfinavir (for HIV infection)
  - azole medicines (for fungal infections)
  - medicines for an infections (like erythromycin or clarithromycin)
  - nefazodone (for depression).

Do not take Quetiapine Film-coated tablets if the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Quetiapine Film-coated tablets.
Take special care with Quetiapine Film-coated tablets

Quetiapine Film-coated tablets should not be taken by elderly people with dementia (loss of brain function). This is because the group of medicines that Quetiapine Film-coated tablets belongs to may increase the risk of stroke, or in some cases the risk of death, in elderly people with dementia.

Before you take your medicine, tell your doctor if:

- You have any health problems (like heart problems or low blood pressure) or you have had a stroke.
- You have problems with your liver, or have ever had a fit (seizure).
- You know that you have had low levels of white blood cells in the past (which may or may not have been caused by other medicines).
- You have diabetes or have a risk of getting diabetes. If you do, your doctor may check your blood sugar levels while you are taking Quetiapine Film-coated tablets.
- You or someone else in your family has a history of blood clots, as medicines like these have been associated with formation of blood clots.

Thoughts of suicide and worsening of your depression

If you are depressed you may sometimes have thoughts of harming or killing yourself. These may be increased when first starting treatment, since these medicines all take time to work, usually about two weeks but sometimes longer. You may be more likely to think like this if you are a young adult. Information from clinical trials has shown an increased risk of suicidal thoughts and/or suicidal behaviour in young adults aged less than 25 years with depression.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away. You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken, any other medicines. This includes medicines that you buy without a prescription and herbal medicines.

In particular, tell your doctor if you are taking any of the following:

- Medicines for anxiety or depression.
- Epilepsy medicines (like phenytoin or carbamazepine)
- High blood pressure medicines
- Rifampicin (for tuberculosis).
- Barbiturates (for difficulty sleeping).
- Thoridazine (another anti-psychotic medicine).

Before you stop taking any of your medicines, please talk to your doctor first.

Taking Quetiapine with food and drink

- Quetiapine Film-coated tablets can be taken with or without food.
- Be careful how much alcohol you drink. This is because the combined effect of Quetiapine and alcohol can make you feel sleepy.
- Do not drink grapefruit juice while you are taking Quetiapine Film-coated tablets. It can affect the way the medicine works.

Pregnancy and breast-feeding

If you are pregnant, trying to get pregnant, or breast-feeding, talk to your doctor before taking Quetiapine Film-coated tablets.

Driving and using machines

Your tablets may make you feel sleepy. You should not drive or use any tools or machines until you know how the tablets affect you.

Hospital - If you go into hospital tell the medical staff that you are taking Quetiapine Film-coated tablets.

Important information about some of the ingredients of Quetiapine Film-coated tablets
Quetiapine Film-coated tablets contains lactose which is a type of sugar. If you have been told by your doctor or pharmacist that you cannot tolerate or digest some sugars, talk to your doctor before taking this medicine.

3. HOW TO TAKE QUETIAPINE FILM-COATED TABLETS

Always take Quetiapine Film-coated tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Your doctor will decide on the starting dose and may gradually increase it. After this the dose will usually be between 150 mg and 800 mg each day. It depends on your illness and needs.

- You will take your tablets once a day, at bedtime or twice a day, depending on your illness.
- Swallow your tablets whole with a drink of water.
- Do not stop taking your tablets even if you feel better, unless your doctor tells you.

Quetiapine Film-coated tablets come in 5 different strengths and each strength is a different colour or shape.

- Even though the dose might stay the same, it might be supplied as different strength tablets. For example, one 300 mg tablet (white) or two 150 mg tablets (pale yellow).
- So don’t be surprised if the colour of your tablets changes from time to time.

Liver problems
If you have liver problems your doctor may give you a lower dose.

Elderly people
If you are elderly your doctor may give you a lower dose.

Children and adolescents under 18 years
Quetiapine Film-coated tablets should not be used in children and adolescents aged under 18 years.

If you take more Quetiapine Film-coated tablets than you should
If you take more Quetiapine Film-coated tablets than prescribed by your doctor, go to your doctor or nearest hospital straight away. Take the Quetiapine Film-coated tablets with you.

If you forget to take Quetiapine
If you forget to take a dose, take it as soon as you remember. If it is almost time to take the next dose, wait until then. Do not take a double dose to make up for a forgotten dose.

If you stop taking Quetiapine
If you suddenly stop taking Quetiapine Film-coated tablets, you may be unable to sleep (insomnia) you may feel sick (nausea), or you may experience headache, diarrhoea, being sick (vomiting), dizziness or irritability. Your doctor may suggest you reduce the dose gradually before stopping treatment.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Quetiapine can cause side effects, although not everybody gets them.

If any of the following happen, stop taking Quetiapine Film-coated tablets and contact a doctor or go to the nearest hospital straight away, as you may need urgent medical attention:

Uncommon (affects less than 1 in 100 people):
- Fits or seizures.
- Allergic reactions that may include raised lumps (weals), swelling of the skin and swelling around the mouth.
- Uncontrollable movements, mainly of your face or tongue (Tardive dyskinesia).

Rare (affects less than 1 in 1,000 people):
• A high temperature (fever), long-lasting sore throat or mouth ulcers, faster breathing, sweating, stiff muscles, feeling very sleepy or faint, large increase in blood pressure or heartbeat.
• Jaundice (yellowing of the skin and eyes).
• Priapism (a long-lasting and painful erection).
• Blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing.

Very rare (affects less than 1 in 10,000 people):
• Severe allergic reaction that may include difficulty in breathing, dizziness and collapse.
• Hepatitis (inflammation of the liver).
• Rapid swelling of the skin, usually around the eyes, lips and throat.

Other possible side effects:

Very common (affects more than 1 in 10 people):
• Dizziness (may lead to falls), headache, dry mouth.
• Feeling sleepy (this may go away with time, as you keep taking Quetiapine Film-coated tablets) (may lead to falls).
• Discontinuation symptoms (symptoms which occur when you stop taking Quetiapine Film-coated tablets) include not being able to sleep (insomnia), feeling sick (nausea), headache, diarrhoea, being sick (vomiting), dizziness and irritability. They usually go away after 1 week from your last dose.
• Putting on weight.

Common (affects less than 1 in 10 people):
• Rapid heartbeat or fainting.
• Stuffy nose.
• Indigestion or constipation.
• Feeling weak (may lead to falls).
• Swelling of arms or legs.
• High blood sugar.
• Low blood pressure when standing. This may make you feel dizzy or faint (may lead to falls).
• Blurred vision.
• Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain.
• Abnormal dreams and nightmares.
• Feeling more hungry.
• Feeling irritated.
• Disturbance in speech or language.

Uncommon (affects less than 1 in 100 people):
• Restless legs.
• Difficulty swallowing.

Rare (affects less than 1 in 1,000 people):
• Swelling of breasts and unexpected production of breast milk (galactorrhoea).

Very rare (affects less than 1 in 10,000 people):
• Worsening of pre-existing diabetes.
• A severe rash, blisters or red patches on the skin.

Some side effects are only seen when a blood test is taken. These include changes in the amount of certain fats (triglycerides and total cholesterol) or sugar in the blood, decreases in the number of certain types of blood cells and increases in the amount of the hormone prolactin in the blood. Increases in the hormone prolactin could in rare cases lead to the following:
• Men and women to have swelling of the breasts and unexpectedly produce breast milk.
• Women to have no monthly period or irregular periods.

Your doctor may ask you to have blood tests from time to time.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Children and adolescents

The same side effects that may occur in adults may also occur in children and adolescents.

The following side effect has been seen only in children and adolescents:
Very Common (affects more than 1 in 10 people):
- Increase in blood pressure.
- The following side effects have been seen more often in children and adolescents:

Very Common (affects more than 1 in 10 people):
- Increase in the amount of a hormone called prolactin, in the blood. Increases in the hormone prolactin could in rare cases lead to the following:
  - boys and girls to have swelling of breasts and unexpectedly produce breast milk
  - girls to have no monthly period or irregular periods.
- Increased appetite.
- Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain.

5. HOW TO STORE QUETIAPINE FILM-COATED TABLETS

- This medicinal product does not require any special storage conditions.
- Keep you Quetiapine Film-coated tablets in a safe place, where children cannot see or reach them.
- Do not use Quetiapine Film-coated tablets after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Quetiapine Film-coated tablets contains

- The active substance is quetiapine as quetiapine fumarate
- The other ingredients are: Microcrystalline cellulose, povidone K29-32, calcium hydrogen phosphate dihydrate, sodium starch glycolate (Type A), lactose monohydrate, magnesium stearate, hypromellose 6cP, macrogol 3350, triacetin, titanium dioxide, iron oxide yellow (E-172) (in 25 mg, 100 mg and 150 mg tablets) and iron oxide red (E-172) (only in the 25 mg tablets).

What Quetiapine Film-coated tablets look like and contents of the pack

Quetiapine 25 mg film-coated tablet is round, biconvex, light orange tablet with the diameter 5.5 mm and engraved with “Q” on one side.
Quetiapine 100 mg film-coated tablet is round, biconvex, yellow tablet with the diameter 8.5 mm and engraved with “Q” on one side.
Quetiapine 150 mg film-coated tablet is oval, biconvex, pale yellow tablet with the diameter 6.9 x 13.8 mm and engraved with “Q” on one side.
Quetiapine 200 mg film-coated tablet is oval, biconvex, white tablet with the diameter 16 x 8.2 mm and engraved with “Q” on one side.
Quetiapine 300 mg film-coated tablet is oval, biconvex, white tablet with the diameter 19 x 7.6 mm, engraved with “Q” on one side and “300” on the other side.

Pack sizes*:
Blisters: 6, 10, 20, 30, 50, 60, 90, 100 tablets
Tablet containers: 6, 10, 20, 30, 50, 60, 90, 100 tablets

*Not all pack sizes may be marketed.

Marketing Authorisation Holder
Caduceus Pharma Ltd
6th Floor
94 Wigmore Street
London
W1U 3RF
Manufacturer
Actavis Ltd.
BLB016 Bulebel Industrial Estate
Zejtun
Malta

Actavis hf.
Reykjavikurvegur 78
220 Hafnarfjordur
Iceland

This leaflet was last revised in 06/2010
The labelling below is the label text agreed at the end of the procedure. The marketing authorisation holder has committed to submit the mock-up of the labels for review to the regulatory authority before marketing the product.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING**

**TABLET CONTAINER and**  
**CARTON for BLISTER and**  
**CARTON for TABLET CONTAINER**

1. **NAME OF THE MEDICINAL PRODUCT**

Quetiapine 25 mg Film-coated Tablets

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 25 mg quetiapine (as fumarate)

3. **LIST OF EXCIPIENTS**

Excipient: Lactose monohydrate, see leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

6 Film-coated Tablets  
10 Film-coated Tablets  
20 Film-coated Tablets  
30 Film-coated Tablets  
50 Film-coated Tablets  
60 Film-coated Tablets  
90 Film-coated Tablets  
100 Film-coated Tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
To be taken as directed by your doctor.  
For oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Caduceus Pharma Limited, 6th Floor, 94 Wigmore Street, London, W1U 3RF

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 24668/0163

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Quetiapine 25 mg Tablets

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

1. **NAME OF THE MEDICINAL PRODUCT**

Quetiapine 25 mg Film-coated Tablets

(Quetiapine fumarate)

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Caduceus Pharma Limited

3. **EXPIRY DATE**

EXP

4. **BATCH NUMBER**

Lot

5. **OTHER**
**UKPAR Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets**

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>TABLET CONTAINER and CARTON for BLISTER and CARTON for TABLET CONTAINER</td>
</tr>
</tbody>
</table>

**1. NAME OF THE MEDICINAL PRODUCT**

Quetiapine 100 mg Film-coated Tablets

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 100 mg quetiapine (as fumarate)

**3. LIST OF EXCIPIENTS**

Excipient: Lactose monohydrate, see leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

| 10 Film-coated Tablets |
| 20 Film-coated Tablets |
| 30 Film-coated Tablets |
| 50 Film-coated Tablets |
| 60 Film-coated Tablets |
| 90 Film-coated Tablets |
| 100 Film-coated Tablets |

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
To be taken as directed by your doctor.
For oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited, 6th Floor, 94 Wigmore Street, London, W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0164

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE


16. INFORMATION IN BRAILLE

Quetiapine 100 mg Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Quetiapine 100 mg Film-coated Tablets

(Quetiapine fumarate)

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

TABLET CONTAINER and
CARTON for BLISTER and
CARTON for TABLET CONTAINER

1. **NAME OF THE MEDICINAL PRODUCT**

Quetiapine 150 mg Film-coated Tablets

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 150 mg quetiapine (as fumarate)

3. **LIST OF EXCIPIENTS**

Excipient: Lactose monohydrate, see leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

6 Film-coated Tablets
10 Film-coated Tablets
20 Film-coated Tablets
30 Film-coated Tablets
50 Film-coated Tablets
60 Film-coated Tablets
90 Film-coated Tablets
100 Film-coated Tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
To be taken as directed by your doctor.
For oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
UKPAR Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets

PL 24668/0163-7

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited, 6th Floor, 94 Wigmore Street, London, W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0165

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Quetiapine 150 mg Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Quetiapine 150 mg Film-coated Tablets

(Que tiapine fumarate)

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER
**UKPAR Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated Tablets**

**PL 24668/0163-7**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING**

TABLET CONTAINER and CARTON for BLISTER and CARTON for TABLET CONTAINER

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**1. NAME OF THE MEDICINAL PRODUCT**

Quetiapine 200 mg Film-coated Tablets

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**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 200 mg quetiapine (as fumarate)

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**3. LIST OF EXCIPIENTS**

Excipient: Lactose monohydrate, see leaflet for further information.

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**4. PHARMACEUTICAL FORM AND CONTENTS**

- 6 Film-coated Tablets
- 10 Film-coated Tablets
- 20 Film-coated Tablets
- 30 Film-coated Tablets
- 50 Film-coated Tablets
- 60 Film-coated Tablets
- 90 Film-coated Tablets
- 100 Film-coated Tablets

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**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
To be taken as directed by your doctor.
For oral use.

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**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

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**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

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**8. EXPIRY DATE**

EXP

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**9. SPECIAL STORAGE CONDITIONS**

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**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited, 6th Floor, 94 Wigmore Street, London, W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0166

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Quetiapine 200 mg Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Quetiapine 200 mg Film-coated Tablets

(Quetiapine fumarate)

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

TABLET CONTAINER and CARTON for BLISTER and CARTON for TABLET CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Quetiapine 300 mg Film-coated Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg quetiapine (as fumarate)

3. LIST OF EXCIPIENTS

Excipient: Lactose monohydrate, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

6 Film-coated Tablets
10 Film-coated Tablets
20 Film-coated Tablets
30 Film-coated Tablets
50 Film-coated Tablets
60 Film-coated Tablets
90 Film-coated Tablets
100 Film-coated Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
To be taken as directed by your doctor.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited, 6th Floor, 94 Wigmore Street, London, W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL 24668/0167

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Quetiapine 300 mg Tablets

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

**1. NAME OF THE MEDICINAL PRODUCT**

Quetiapine 300 mg Film-coated Tablets

(Quetiapine fumarate)

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Caduceus Pharma Limited

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**