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

PL 14894/0540

PL 14894/0542-5

UKPAR

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The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated tablets (Product Licence numbers: PL 14894/0540 and PL 14894/0542-5) on 17 August 2010.

Quetiapine tablets help to control the symptoms of a mental illness called schizophrenia. The symptoms of schizophrenia include delusions (having strange or unusual thoughts), hallucinations (seeing or hearing things that are not there), experiencing unusual behaviour, which can be aggressive and becoming withdrawn and subdued.

Quetiapine tablets may be used for the treatment of manic episodes. These episodes cause periods of excessive cheerfulness and increased activity. People with this condition may become unusually irritable, need less sleep than normal and have quickly changing thoughts. This is known as bipolar mania.

Quetiapine tablets may be used in the treatment of 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 known as bipolar depression.

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

Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated tablets to Ranbaxy (UK) Ltd on 17 August 2010. These medicines are only available on prescription.

Quetiapine is indicated for the treatment of schizophrenia and bipolar disorder (including manic episodes associated with bipolar disorder, major depressive episodes in bipolar disorder and preventing recurrence in bipolar disorder in patients whose manic, mixed or depressive episode has responded to quetiapine treatment).

These applications are submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applicant claims that Quetiapine 25mg, 100mg, 150mg, 200mg and 300mg Film-coated tablets are generic versions of Seroquel 25 mg, 100 mg, 150 mg, 200 mg and 300 mg film-coated tablets (PL 17901/0038-41 and PL 17901/0088), which are marketed by AstraZeneca UK Ltd. Seroquel tablets were first authorised in the UK on 31 July 1997, the legal basis of these applications is, therefore, acceptable and the ten year rule is complied with.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE: QUETIAPINE

Manufacture
The method of manufacture of quetiapine is appropriate.

Control of Drug Substance
The proposed drug substance specification and its justification, analytical procedures and their validation, batch analyses and reference standards used by the drug substance manufacturer are satisfactory.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Container Closure System
The drug substance quetiapine is stored in appropriate packaging. The specifications and typical analytical test reports for the packaging are provided and are satisfactory.

Stability
Appropriate stability data have been generated supporting the retest period.

DRUG PRODUCT

Composition
The tablets contain the excipients calcium hydrogen phosphate (dihydrate), lactose monohydrate, microcrystalline cellulose, povidone (PVP K30), sodium starch glycollate (Type A) and magnesium stearate. In addition the film coating of the 25mg tablets contain Opadry 03B52874 Yellow (hypromellose 6cP (E464), titanium dioxide (E171), macrogol /PEG 4000, iron oxide yellow (E172) and iron oxide red (E172) and the film coating of the 100mg, 150mg, 200mg and 300mg tablets contain Opadry OYS-58910 White (hypromellose 5cP (E464), titanium dioxide (E171), macrogol /PEG 400 and talc (E553b).

Satisfactory certificates of analysis have been provided for all excipients. All of the tablet core excipients are Ph Eur and were tested in line with their Ph Eur monographs. The Opadry formulations used for film-coating are constituted from pharmacopeial ingredients, along with widely used colourants that comply with Directive 95/45/EC. Suitable in-house specifications, accompanied by analytical methodology, are presented for each Opadry formulation.

There were no novel excipients used and no overages. A declaration is provided by the supplier of lactose monohydrate confirming that the lactose is sourced from milk from healthy cows under the same conditions as milk for human consumption and that calf rennet used in the processing is in accordance with the CPMP/BWP statement of 27 February 2002. Declarations from the suppliers of the remaining excipients have been provided, which confirm that the respective materials are not of animal origin.
Pharmaceutical Development
The objective of the development programme was to formulate robust, stable tablets that contain qualitatively and quantitatively the same active ingredient as Seroquel 25 mg, 100 mg, 150 mg, 200 mg and 300 mg film-coated, and exhibiting the same bioavailability in order to comply with the regulations pertaining to generic medicinal product applications. A satisfactory account of the pharmaceutical development has been provided.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each tablet strength. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
Quetiapine tablets are stored in blister packs of PVC/PE/PVdC/Al or PVC/ACLAR. The 25mg and 300mg tablets are stored in packs of 6, 10, 20, 30, 50, 60 or 100 tablets. The 100mg tablets are stored in packs of 3, 20, 30, 60, 50 or 100 tablets. The 150mg tablets are stored in packs of 20, 60 or 30 tablets. The 200mg tablets are stored in packs of 1, 10, 60, 20, 30, 50, 90 or 100 tablets.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. This medicinal product does not require any special storage conditions.

Product literature
All product literature (SPCs, PIL and labelling) are satisfactory. The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
INTRODUCTION

Clinical Background
Quetiapine is an antipsychotic agent which combines potent serotonin (5-hydroxytryptamine) 5-HT2 and dopamine D2 receptor antagonism. The pharmacokinetics of quetiapine are well understood, having been studied in healthy young and elderly subjects as well as in psychotic patients.

Indications
The following indications are proposed:

“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.”

These indications are in line with those of the reference product and are satisfactory.

Dose and Dose Regimen
The following dose and dose regimen is proposed:

“Quetiapine can be administered with or without food.

Adults
For the treatment of schizophrenia: Quetiapine should be administered twice daily. 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 therapy to mood stabilizers, 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. 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, the
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 should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on Quetiapine 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**
Dosage 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 dosing 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.”

This is in line with the dose and dose regimen for the reference product and is satisfactory.

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**
Pharmacotherapeutic group: Antipsychotics
ATC code: N05A H04

**Mechanism of action**
Quetiapine is an atypical antipsychotic agent.

Quetiapine and the active human plasma metabolite, \(N\)-desalkyl quetiapine, interact with a broad range of neurotransmitter receptors. Quetiapine and \(N\)-desalkyl
Quetiapine exhibit affinity for brain serotonin 5-HT\textsubscript{2} and dopamine D\textsubscript{1} and D\textsubscript{2} receptors. Quetiapine exhibits a higher affinity for serotonin 5-HT\textsubscript{2} receptors in the brain than it does for dopamine D\textsubscript{1} and D\textsubscript{2} receptors in the brain. Additionally, N-desalkyl quetiapine has high affinity at serotonin 5-HT\textsubscript{1} receptors. Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic \(\alpha\) receptors, with a lower affinity at adrenergic \(\alpha\)-receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. The extent to which the N-desalkyl quetiapine metabolite contributes to the pharmacological activity of quetiapine in humans is not known.

**Pharmacodynamic effect**

The results of animal studies predictive of extrapyramidal symptom (EPS) liability revealed that quetiapine causes only weak catalepsy at effective dopamine D\textsubscript{2} receptor blocking doses, that quetiapine causes selective reduction in the firing of mesolimbic A\textsubscript{10} dopaminergic neurones versus the A\textsubscript{9} nigrostriatal neurones involved in motor function, and that quetiapine exhibits minimal dystonic liability in neuroleptic sensitised monkeys.

**Pharmacokinetics**

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 N-desalkyl quetiapine are 35% of that observed for quetiapine. The elimination half-lives of quetiapine and N-desalkyl quetiapine are approximately 7 and 12 hours, respectively.

**Bioequivalence study**

An open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover study was carried out to assess the bioavailability of Quetiapine 25 mg Film-coated tablets in comparison with Seroquel 25 mg film-coated tablets (AstraZenica).

The lowest dose of 25 mg was selected because of safety concerns if healthy subjects were used for 100 mg (or higher strength) testing. Alternatives, such as titrating up to a steady state or using higher doses in patients, would, on balance, be less satisfactory.

**Biowaver**

A waiver in respect of the other strengths appears reasonable given the applicant’s justification, which is in line with the CPMP Note for Guidance on Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the following conditions having been met:

1. the pharmaceutical products are manufactured by the same manufacturer and process
2. the drug input has been shown to be linear over the therapeutic dose range
3. the qualitative composition of the different strengths is the same
4. the ratio between amounts of active ingredient and excipients is the same, or, in the case of preparations containing a low concentration of the active substance (less than 5%), the ratio between the amounts of excipients is similar
5. the dissolution profile is similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

**Good Clinical Practice (GCP) and Good Laboratory Practice (GLP)**
The clinical overview states that the bioequivalence study was conducted according the GCP and GLP guidelines. A certificate of GCP/GLP compliance is provided as well as a quality assurance authentification.

**Study design**
The study subjects were healthy, fasted, male, adult volunteers. No interaction with food is reported for quetiapine, therefore, the use of fasted subjects is appropriate. Steady-state peak molar concentrations of the active metabolite N-desalkyl quetiapine are 35% of that observed for quetiapine. The pharmacokinetics of quetiapine and N-desalkyl quetiapine are linear across the 50mg – 800mg dose range. As there is no clinically significant active metabolite for quetiapine, the study design is satisfactory for this product.

**Number of subjects studied**
A total of 32 volunteers were enrolled in the study and 29 subjects completed the study. Analysis was performed on all samples collected from the 29 subjects and statistical analysis was performed.

**Dose administered (test/reference)**
A single oral dose of the reference (Seroquel 25 mg film-coated tablets) or test formulation (Quetiapine 25mg Film-coated tablets) was administered under low light condition after an overnight fast as per the randomization schedule. Subjects received the alternate ‘treatment’ in the subsequent periods, in such a way that each subject received both the formulations by the end of the study. All subjects were required to fast overnight after admission for at least 10 hours before the morning dose and for 4 hours post dose.

**Pre-defined bioequivalence acceptance criteria**
The protocol defines acceptance criteria of 0.8 – 1.25 for both AUC and Cmax. This is satisfactory.

**Sampling**
A total of forty 5 mL (except pre-dose sample which was 2 x 5 mL) blood samples were collected from each subject under low light conditions in EDTA vacutainers during the course of the study through indwelling cannulae placed in forearm veins. Blood samples were collected pre-dose and up to 24 hours post dose in each period. Adverse events and vital signs have been monitored at the specified time-points during this study.

The duration of sampling following dosing is sufficient for AUCt > 80% of AUCinf, and the sampling frequency around Tmax is adequate for accurate Cmax estimation.

**Washout period**
Each period was separated by a period of 7 days.

**Randomisation scheme**
Block of eight, random.
Pharmacokinetic parameters
The following parameters have been estimated.
- **Cmax**: Maximum measured plasma concentration over the time span specified.
- **Tmax**: Time of the maximum measured plasma concentration.
- **AUC0-t**: The area under the plasma concentration versus time curve, from time zero to the last measurable concentration, as calculated by the linear trapezoidal method.
- **AUC0-∞**: The area under the plasma concentration versus time curve, from time zero to infinity.
- **Kel**: Apparent first-order terminal elimination rate constant calculated from a semilog plot of the plasma concentration versus time curve.
- **t1/2**: The apparent first-order terminal elimination half-life were calculated as 0.693/Kel.

Method of data analysis
Analysis of Variance (ANOVA) was performed on the log (natural)-transformed pharmacokinetic parameters (Cmax, AUC0-t, AUC0-∞) for quetiapine using Type III sum of squares, with the main effects of sequence, period and formulations as fixed effects and subjects nested within sequence as random effect. The sequence effect was tested at 10% level of significance using the subjects nested within sequence mean square as the error term. All other main effects were tested at the 5% level of significance against the residual error (mean square error) from the ANOVA model as the error term.

Results
Thirty-two healthy adult male subjects were enrolled into the study and twenty-nine subjects completed both the periods of the study. The mean age of enrolled subjects was 25 years (range: 19-38 years).

Results for main pharmacokinetic parameters:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (h)</th>
<th>AUC0-t (ng.h/mL)</th>
<th>AUC0-∞ (ng.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>T</td>
<td>R</td>
<td>T</td>
</tr>
<tr>
<td>Mean</td>
<td>152.228</td>
<td>157.290</td>
<td>1.1322</td>
<td>1.0529</td>
</tr>
<tr>
<td>SD</td>
<td>69.9510</td>
<td>62.2218</td>
<td>0.74385</td>
<td>0.59724</td>
</tr>
<tr>
<td>CV%</td>
<td>46.0</td>
<td>39.6</td>
<td>65.7</td>
<td>56.7</td>
</tr>
<tr>
<td>N</td>
<td>29</td>
<td>29</td>
<td>29</td>
<td>29</td>
</tr>
</tbody>
</table>

R: Seroquel 25 mg tablet
T: Quetiapine tablets 25 mg
N: number of observations

Although the pharmacokinetic parameters obtained in the study were higher than that reported in some literature (possibly due to differential polymorphism in the CYP3A group of enzymes that metabolise quetiapine), as the study was designed and conducted as per relevant regulatory and scientific principles, this does not impact upon the bioequivalence conclusions.
Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

<table>
<thead>
<tr>
<th>Ratio of lSM (90% Confidence Intervals)</th>
<th>Parameters</th>
<th>Quetiapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>ln Cmax</td>
<td>106.07 % (93.45 - 120.39 %)</td>
<td></td>
</tr>
<tr>
<td>ln AUC0-1</td>
<td>101.70 % (90.88 - 113.81%)</td>
<td></td>
</tr>
<tr>
<td>ln AUC0-∞</td>
<td>101.65 % (91.13 - 113.38%)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion on Bioequivalence
The study design was appropriate to study equivalence between the two tablets. Bioequivalence is considered to be shown.

CLINICAL EFFICACY AND SAFETY

Efficacy
Quetiapine is a well-established agent used for the treatment of schizophrenia and manic episodes associated with bipolar disorder. Its efficacy and safety in these indications have been extensively demonstrated in clinical trials and postmarketing use.

Safety
The test and reference products were well tolerated. A total of 26 adverse events (AE) were observed in the study, out of which one was a pre-dose AE. Out of the 25 post-dose AEs, six were observed in the reference group in period I, nine in the test group in period I, five in the reference group in period II, and five in the test group in period II.

The adverse effects that were reported during the bioequivalence study were expected and do not raise specific safety concern.

Pharmacovigilance System
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant 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 either in the Community or in a third country.

Risk Management Plan
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.

Expert report
The clinical expert has provided an adequate overview of efficacy and safety of these products.
**Risk Benefit**
The risk benefit balance for this application is positive.

**Conclusion**
It is recommended that Marketing Authorisations are granted 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.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The efficacy of quetiapine is well established. The SPCs, PIL and labelling are satisfactory and consistent with those for the cross-reference product.

SAFETY
No new safety data have been submitted with these applications. As the safety profile of quetiapine is well-known, this is satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with buprenorphine. The risk benefit is therefore considered to be positive.
<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation applications on 19 December 2007</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 21 January 2008</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 3 June 2008 and the quality dossier on 24 June 2008</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 17 September 2008 and the clinical dossier on 3 October 2008</td>
</tr>
<tr>
<td>5</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 3 October 2008 and the clinical dossier on 14 January 2009</td>
</tr>
<tr>
<td>6</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 5 November 2008 and the clinical dossier on 3 March 2009</td>
</tr>
<tr>
<td>7</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 8 January 2009</td>
</tr>
<tr>
<td>8</td>
<td>The applicant responded to the MHRA’s request, providing further information on the quality dossier on 18 April 2009</td>
</tr>
<tr>
<td>9</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 25 June 2009 and the clinical dossier on 10 March 2010</td>
</tr>
<tr>
<td>10</td>
<td>The applicant responded to the MHRA’s request, providing further information on the quality dossier on 25 August 2009 and the clinical dossier 11 May 2010</td>
</tr>
<tr>
<td>11</td>
<td>The applications were determined on 17 August 2010</td>
</tr>
</tbody>
</table>
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)
This tablet also contains Lactose monohydrate.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film Coated Tablet

Peach coloured, round tablets debossed with ‘Q1’ on one side and plain 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 can be administered with or without food.

Adults
For the treatment of schizophrenia: Quetiapine should be administered twice daily. 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 therapy to mood stabilizers, 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. 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, the 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 should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on Quetiapine 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
Dosage 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 dosing 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**

Hypersensitivity to the active substance or to any of the excipients 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).

4.4 **Special warnings and precautions for use**

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

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. Clinical trials have shown that in addition to the known safety profile identified in adults (see section 4.8), 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).

**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 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.

**QT Prolongation**
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. 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).

**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.

**Extrapyramidal symptoms**
In placebo controlled clinical trials 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).

**Tardive dyskinesia**
As with other antipsychotics, there is a potential for quetiapine to cause tardive dyskinesia after long-term treatment. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered.

**Neuroleptic malignant syndrome**
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including Quetiapine (see Section 4.8). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, Quetiapine 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 is no apparent dose relationship.
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 4.8).

**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).

**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 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).

**Elderly patients with dementia-related psychosis**
Quetiapine is not approved for the treatment of dementia-related psychosis. An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo-controlled 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 risk factors for stroke.

**Hepatic effects**
If jaundice develops, quetiapine should be discontinued.

**Lipids**
Increases in triglycerides and cholesterol have been observed in clinical trials with quetiapine (see Section 4.8 Undesirable effects). Lipid increases should be managed as clinically appropriate.

**Lactose**
This medicinal product contains lactose monohydrate. 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 or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 and 5.1). 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, Quetiapine should be used with caution in combination with other centrally acting drugs and alcohol.

The pharmacokinetics of lithium was 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 (quetiapine fumarate). Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.

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

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 (as 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, and hence, in each patient, consideration for a higher dose of quetiapine, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of quetiapine is 750mg/day for the treatment of schizophrenia and 800mg/day for the treatment of manic episodes associated with bipolar disorder. Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit risk assessment for an individual patient. Co-administration of quetiapine with another microsomal enzyme inducer, phenytoin, also caused increases in the clearance of quetiapine. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and phenytoin and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc.). The dose of quetiapine may need to be reduced if phenytoin or
carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. The pharmacokinetics of quetiapine was not altered following co-administration with cimetidine, a known P450 enzyme inhibitor. The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor). However, caution is recommended when quetiapine is co-administered with potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors). (See also Section 4.4 Special Warnings & Special Precautions for Use and Section 5.2 Pharmacokinetics.)

Caution should be exercised when quetiapine is used concomitantly with agents 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 harmfullness 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.

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. 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 Quetapine are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension, and dyspepsia.
As with other antipsychotics, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with quetiapine.
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
<table>
<thead>
<tr>
<th>Common</th>
<th>Leucopenia(^1)</th>
<th>Eosinophilia, Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td></td>
<td>Neutropenia(^1)</td>
</tr>
</tbody>
</table>

### Immune system disorders

<table>
<thead>
<tr>
<th>Uncommon</th>
<th>Hypersensitivity</th>
<th>Anaphylactic reaction(^6)</th>
</tr>
</thead>
</table>

### Endocrine disorders

<table>
<thead>
<tr>
<th>Common</th>
<th>Hyperprolactinaemia(^1,6)</th>
</tr>
</thead>
</table>

### Metabolism and nutritional disorders

<table>
<thead>
<tr>
<th>Common</th>
<th>Increased appetite</th>
<th>Diabetes mellitus(^1,5,6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Psychiatric disorders

<table>
<thead>
<tr>
<th>Common</th>
<th>Abnormal dreams and nightmares</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Dizziness(^4,17), Somnolence(^2,17), Headache</td>
</tr>
<tr>
<td>Common</td>
<td>Syncope(^4,7)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Extrapyramidal symptoms(^1,13)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Seizure(^1), Restless legs syndrome,</td>
</tr>
<tr>
<td>Common</td>
<td>Dysarthria, Tardive dyskinesia(^6)</td>
</tr>
<tr>
<td></td>
<td>Tachycardia(^4)</td>
</tr>
</tbody>
</table>

### Eye disorders

| Common                                  | Vision blurred              |
|                                        |                              |

### Vascular disorders

| Common                                  | Orthostatic hypotension\(^4,17\) |
|                                        | Rhinitis                      |

### Respiratory thoracic and mediastinal disorder

| Common                                  |                              |
|                                        | Dry mouth                    |

### Gastrointestinal disorder

| Very                                    | Constipation, dyspepsia   |
| Common                                  |                             |
| 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 (predominately LDL cholesterol)\(^12\), 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\(^15\)

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(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 quetiapine.
(3) Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine.
(4) As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine 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 ≥7.0mmol/L or a non fasting blood glucose ≥11.1mmol/L on at least one occasion.
(8) An increase in the rate of dysphagia with quetiapine 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.
(10) The following withdrawal symptoms have been observed most frequently in acute placebocontrolled, 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 (≥2.258mmol/L) on at least one occasion.
(12) Cholesterol ≥240mg/dL (≥6.2064mmol/L) on at least one occasion. An increase in LDL cholesterol of ≥30mg/dL (_0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7mg/dL (_1.07mmol/L).
(13) See text below.
(14) Platelets ≤100 x 109/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): >20μg/L (>869.56pmol/L) males; >30μg/L (>1304.34pmol/L) females at any time.
(17) May lead to falls.
(18) HDL cholesterol: <40 mg/dL (1.025mmol/L) males; <50 mg/dL (1.282mmol/L) females at any time.

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

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 shortterm, 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 adolescents 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\(^4\)

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1. Prolactin levels (patients < 18 years of age): >20 ug/L (>869.56 pmol/L) males; >26 ug/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 ug/L.
2. Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20mmHg 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 5.1
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 postmarketing 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 active substance's known pharmacological effects, 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).

**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: N05A H04

Mechanism of action
Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin (5HT$_2$) and dopamine D$_1$ and D$_2$ receptors. Quetiapine exhibits a higher affinity for serotonin (5HT$_2$) receptors in the brain than it does for dopamine D$_1$ and D$_2$ receptors in the brain. Additionally, N-desalkyl quetiapine has high affinity for norepinephrine transporter (NET). Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic $\alpha_1$ receptors, with a lower affinity at adrenergic $\alpha_2$-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 depolarization blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurons following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naïve 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 antidepressant 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 antidepressant 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 totaling 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 \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 sections 4.4 and 4.8).

**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 N-desalkyl quetiapine are 35% of that observed for quetiapine. The elimination half-lives of quetiapine and N-desalkyl quetiapine 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 N-desalkyl quetiapine 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) and in subjects with hepatic impairment (stable alcoholic cirrhosis), 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 N-desalkyl quetiapine 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.
In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. N-desalkyl quetiapine 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 N-desalkyl quetiapine) 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 medicinal products will result in clinically significant inhibition of cytochrome P450-mediated metabolism of the other drug.

**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 cynomologus 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**

*Intragranular*

Calcium hydrogen phosphate (Dihydrate),

Lactose monohydrate,
Microcrystalline cellulose, 
Povidone (PVP K30), 

*Extrargranular*
Sodium starch glycollate (Type A), 
Magnesium stearate, 

*Film coating material composition*
Opadry 03B52874 Yellow containing:
Hypromellose 6cP (E464) 
Titanium dioxide (E171) 
Macrogol /PEG 4000 
Iron oxide yellow (E172) 
Iron oxide red (E172)

6.2 **Incompatibilities**
Not applicable

6.3 **Shelf life**
2 years.

6.4 **Special precautions for storage**
This medicinal product does not require any special storage condition.

6.5 **Nature and contents of container**
Blister pack of PVC/PE/PVdC/Al 
Or 
Blister pack of PVC/ACLAR 
Pack sizes: 6, 10, 20, 30, 50, 60, 100 
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements 
Any unused product or waste material should be disposed of in accordance with local requirements

7 **MARKETING AUTHORISATION HOLDER**
Ranbaxy (UK) Ltd.,
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 14894/0540
9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/08/2010

10  DATE OF REVISION OF THE TEXT
17/08/2010

1  NAME OF THE MEDICINAL PRODUCT
Quetiapine 100mg Film-coated tablets.

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

For a full list of excipients, see Section 6.1.

3  PHARMACEUTICAL FORM
Film Coated Tablet

White coloured, round tablets debossed with ‘Q3’ on one side and plain 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 can be administered with or without food.

Adults
For the treatment of schizophrenia: Quetiapine should be administered twice daily. 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
therapy to mood stabilizers, 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. 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, the 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 should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on Quetaipine 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**
Dosage 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 dosing 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
Hypersensitivity to the active substance or to any of the excipients of this product.
Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIVprotease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated. (See also section 4.5).

4.4 Special warnings and precautions for use

Children and adolescents (10 to 17 years of age)
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. Clinical trials have shown that in addition to the known safety profile identified in adults (see section 4.8), 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).

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 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.

**QT Prolongation**
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. 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).

**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.

**Extrapyramidal symptoms**
In placebo controlled clinical trials 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**
As with other antipsychotics, there is a potential for quetiapine to cause tardive dyskinesia after long-term treatment. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered.

**Neuroleptic malignant syndrome**
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine (see Section 4.8). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, quetiapine 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 is no apparent dose relationship.
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 4.8).

**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).

**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 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).

**Elderly patients with dementia-related psychosis**
Quetiapine is not approved for the treatment of dementia-related psychosis. An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo-controlled 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 risk factors for stroke.

**Hepatic effects**
If jaundice develops, quetiapine should be discontinued.

**Lipids**
Increases in triglycerides and cholesterol have been observed in clinical trials with quetiapine (see Section 4.8 Undesirable effects). Lipid increases should be managed as clinically appropriate.

**Lactose**
This medicinal product contains lactose monohydrate. 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 or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 and 5.1). 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, Quetiapine should be used with caution in combination with other centrally acting drugs and alcohol.

The pharmacokinetics of lithium was 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 (quetiapine fumarate). Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.

The pharmacokinetics of quetiapine was 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.

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 (as 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, and hence, in each patient, consideration for a higher dose of quetiapine, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of quetiapine is 750mg/day for the treatment of schizophrenia and 800mg/day for the treatment of manic episodes associated with bipolar disorder. Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit risk assessment for an individual patient. Co-administration of quetiapine with another microsomal enzyme inducer, phenytoin, also caused increases in the clearance of quetiapine. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and phenytoin and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc.). The dose of quetiapine may need to be reduced if phenytoin or
carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. The pharmacokinetics of quetiapine was not altered following co-administration with cimetidine, a known P450 enzyme inhibitor. The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor). However, caution is recommended when quetiapine is co-administered with potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors). (See also Section 4.4 Special Warnings & Special Precautions for Use and Section 5.2 Pharmacokinetics.) Caution should be exercised when quetiapine is used concomitantly with agents 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.

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. 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 are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension, and dyspepsia. As with other antipsychotics, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with quetiapine. 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.

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
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<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Leucopenia¹</td>
</tr>
<tr>
<td>System</td>
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<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
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<tr>
<td><strong>Endocrine disorders</strong></td>
</tr>
<tr>
<td><strong>Metabolism and nutritional disorders</strong></td>
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<tr>
<td><strong>Psychiatric disorders</strong></td>
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<tr>
<td><strong>Nervous system disorders</strong></td>
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<td></td>
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<tr>
<td><strong>Cardiac disorders</strong></td>
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<td><strong>Eye disorders</strong></td>
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<tr>
<td><strong>Vascular disorders</strong></td>
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<tr>
<td><strong>Respiratory thoracic and mediastinal disorder</strong></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorder</strong></td>
</tr>
<tr>
<td><strong>Hepato-biliary disorders</strong></td>
</tr>
</tbody>
</table>
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 (predominately LDL 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

(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 quetiapine.

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

(4) As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine 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 ≥7.0mmol/L or a non fasting blood glucose ≥11.1mmol/L on at least one occasion.
(8) An increase in the rate of dysphagia with quetiapine 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.

(10) The following withdrawal symptoms have been observed most frequently in acute placebocontrolled, 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) on at least one occasion.

(12) Cholesterol ≥240 mg/dL (≥6.2064 mmol/L) 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 very rarely with the use of neuroleptics and are considered class effects (see Section 4.4).

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 shortterm, 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 adolescents 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 ug/L (>869.56 pmol/L) males; >26 ug/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 ug/L.
2. Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20mmHg 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 5.1
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 postmarketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma or QT-prolongation. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See section 4.4).

**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: N05A H04

Mechanism of action
Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin (5HT<sub>2</sub>) and dopamine D<sub>1</sub> and D<sub>2</sub> receptors. Quetiapine exhibits a higher affinity for serotonin (5HT<sub>2</sub>) receptors in the brain than it does for dopamine D<sub>1</sub> and D<sub>2</sub> receptors in the brain. Additionally, N-desalkyl quetiapine has high affinity for norepinephrine transporter (NET). Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic α<sub>1</sub> receptors, with a lower affinity at adrenergic α<sub>2</sub>-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 depolarization blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurons following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naïve 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 antidepressant 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 antidepressant 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 totaling 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 sections 4.4 and 4.8).

**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 N-desalkyl quetiapine are 35% of that observed for quetiapine. The elimination half-lives of quetiapine and N-desalkyl quetiapine 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 N-desalkyl quetiapine 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) and in subjects with hepatic impairment (stable alcoholic cirrhosis), 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 N-desalkyl quetiapine 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. 

*In vitro* investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. N-desalkyl quetiapine 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 N-desalkyl quetiapine) 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 medicinal products will result in clinically significant inhibition of cytochrome P450-mediated metabolism of the other drug.

**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 cynomolgous 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

*Intragranular*

- Calcium hydrogen phosphate (Dihydrate),
- Lactose monohydrate,
Microcrystalline cellulose,
Povidone (PVP K30),

_Extra granular_
Sodium starch glycollate (Type A),
Magnesium stearate,

_Film coating material composition_
Opadry OY-S-58910 White containing:
Hypromellose 5eP (E464)
Titanium dioxide (E171)
Macrogol /PEG 400
Talc (E553b)

6.2 **Incompatibilities**
Not applicable

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
This medicinal product does not require any special storage condition.

6.5 **Nature and contents of container**
Blister pack of PVC/PE/PVdC/Al
Or
Blister pack of PVC/ACLAR
Pack sizes: 3, 20, 30, 60, 50 and 100

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements

Any unused product or waste material should be disposed of in accordance with local requirements

7 **MARKETING AUTHORISATION HOLDER**
Ranbaxy (UK) Ltd.,
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 14894/0542
1 NAME OF THE MEDICINAL PRODUCT
Quetiapine 150mg Film-coated tablets.

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

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film Coated Tablet

White coloured, round tablets debossed with ‘Q4’ on one side and plain 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 can be administered with or without food.

Adults
For the treatment of schizophrenia: Quetiapine should be administered twice daily. 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 therapy to mood stabilizers, 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. 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, the 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 should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on Quetiapine 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**

Dosage 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 dosing 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
Hypersensitivity to the active substance or to any of the excipients of this product.
Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIVprotease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated. (See also section 4.5).

4.4 Special warnings and precautions for use

Children and adolescents (10 to 17 years of age)
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. Clinical trials have shown that in addition to the known safety profile identified in adults (see section 4.8), 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).

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 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.

QT Prolongation
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. 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).

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.

Extrapyramidal symptoms
In placebo controlled clinical trials 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).

Tardive dyskinesia
As with other antipsychotics, there is a potential for quetiapine to cause tardive dyskinesia after long-term treatment. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered.

Neuroleptic malignant syndrome
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine (see Section 4.8). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, quetiapine 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 is no apparent dose relationship. 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 4.8).

**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).

**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 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).

**Elderly patients with dementia-related psychosis**
Quetiapine is not approved for the treatment of dementia-related psychosis. An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo-controlled 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 risk factors for stroke.

**Hepatic effects**
If jaundice develops, quetiapine should be discontinued.

**Lipids**
Increases in triglycerides and cholesterol have been observed in clinical trials with quetiapine (see Section 4.8 Undesirable effects). Lipid increases should be managed as clinically appropriate.
**Lactose**

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Additional information**

Quetipaine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 and 5.1). 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, Quetiapine should be used with caution in combination with other centrally acting drugs and alcohol.

The pharmacokinetics of lithium was 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 (quetiapine fumarate). Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.

The pharmacokinetics of quetiapine was 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.

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 (as 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, and hence, in each patient, consideration for a higher dose of quetiapine, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of quetiapine is 750mg/day for the treatment of schizophrenia and 800mg/day for the treatment of manic episodes associated with bipolar disorder. Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit risk assessment for an individual patient. Co-administration of quetiapine with another microsomal enzyme inducer, phenytoin, also caused increases in the clearance of quetiapine. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and phenytoin and other hepatic enzyme inducers (e.g. barbiturates, rifampicin...
etc.). The dose of quetiapine may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. The pharmacokinetics of quetiapine was not altered following co-administration with cimetidine, a known P450 enzyme inhibitor. The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor). However, caution is recommended when quetiapine is co-administered with potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors). (See also Section 4.4 Special Warnings & Special Precautions for Use and Section 5.2 Pharmacokinetics.) Caution should be exercised when quetiapine is used concomitantly with agents 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.

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. 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 are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension, and dyspepsia. As with other antipsychotics, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with quetiapine.

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 \((\geq 1/10)\), 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**
<table>
<thead>
<tr>
<th>Common</th>
<th>Leucopenia&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Eosinophilia, Thrombocytopenia</td>
</tr>
<tr>
<td>Unknown</td>
<td>Neutropenia&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Anaphylactic reaction&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Very rare</td>
<td>Hyperprolactinaemia&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Increased appetite</td>
</tr>
<tr>
<td>Common</td>
<td>Diabetes mellitus&lt;sup&gt;1,5,6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Metabolism and nutritional disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Abnormal dreams and nightmares</td>
</tr>
<tr>
<td>Very rare</td>
<td>Dizziness&lt;sup&gt;4,17&lt;/sup&gt;, Somnolence&lt;sup&gt;2,17&lt;/sup&gt;, Headache</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Syncope&lt;sup&gt;4,7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Common</td>
<td>Extrapyramidal symptoms&lt;sup&gt;1,13&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Seizure&lt;sup&gt;1&lt;/sup&gt;, Restless legs syndrome,</td>
</tr>
<tr>
<td>Very common</td>
<td>Dysarthria, Tardive dyskinesia&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Cardiac disorders</td>
</tr>
<tr>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Tachycardia&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Common</td>
<td>Vision blurred</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Orthostatic hypotension&lt;sup&gt;4,17&lt;/sup&gt;</td>
</tr>
<tr>
<td>Common</td>
<td>Rhinitis</td>
</tr>
<tr>
<td>Respiratory thoracic and mediastinal disorder</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>Constipation, dyspepsia</td>
</tr>
<tr>
<td>Very</td>
<td>Dysphagia&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Common</td>
<td>Jaundice&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hepatitis&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Angioedema&lt;sup&gt;6&lt;/sup&gt;, Stevens-Johnson syndrome&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rare</td>
<td>Priapism, galactorrhoea</td>
</tr>
<tr>
<td>Very rare</td>
<td>Withdrawal (discontinuation) symptoms&lt;sup&gt;1,10&lt;/sup&gt;, Mild asthenia, peripheral oedema, irritability</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Neuroleptic malignant syndrome&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Very rare</td>
<td>Elevations in serum triglyceride levels&lt;sup&gt;11&lt;/sup&gt;,</td>
</tr>
</tbody>
</table>
elevations in total cholesterol (predominately LDL cholesterol) \(^{12}\), 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\(^{15}\)

(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 quetiapine.
(3) Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine.
(4) As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine 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 ≥7.0mmol/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 quetiapine 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.
(10) The following withdrawal symptoms have been observed most frequently in acute placebocontrolled, 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 (≥2.258mmol/L) on at least one occasion.
(12) Cholesterol ≥240mg/dL (≥6.2064mmol/L) on at least one occasion. An increase in LDL cholesterol of ≥30mg/dL (_0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7mg/dL (_1.07mmol/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): >20μg/L (>869.56pmol/L) males; >30μg/L (>1304.34pmol/L) females at any time.
(17) May lead to falls.
(18) HDL cholesterol: <40 mg/dL (1.025mmol/L) males; <50 mg/dL (1.282mmol/L) females at any time.
Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported very rarely with the use of neuroleptics and are considered class effects (see Section 4.4).

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 adolescents 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).

<table>
<thead>
<tr>
<th>Metabolism and nutritional disorders</th>
<th>Very common</th>
<th>Increased appetite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Very common</td>
<td>Elevations in prolactin(^1), increases in blood pressure(^2)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Extrapyramidal symptoms(^3)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Irritability(^4)</td>
</tr>
</tbody>
</table>
1. Prolactin levels (patients < 18 years of age): >20 ug/L (>869.56 pmol/L) males; >26 ug/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 ug/L.

2. Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20mmHg 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 5.1

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 postmarketing 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 active substance's known pharmacological effects, 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).

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: N05A H04
Mechanism of action

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin (5HT₂) and dopamine D₁ and D₂ receptors. Quetiapine exhibits a higher affinity for serotonin (5HT₂) receptors in the
brain than it does for dopamine D₁ and D₂ receptors in the brain. Additionally, N-desalkyl quetiapine has high affinity for norepinephrine transporter (NET). Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic α₁ receptors, with a lower affinity at adrenergic α₂-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 depolarization blockade of the A₁₀ mesolimbic but not the A₉ nigrostriatal dopamine-containing neurons following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naïve 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 antidepressant 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 antidepressant 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 totaling 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 sections 4.4 and 4.8).

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 N-desalkyl quetiapine are 35% of that observed for quetiapine. The elimination half-lives of quetiapine and N-desalkyl quetiapine 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 N-desalkyl quetiapine 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) and in subjects with hepatic impairment (stable alcoholic cirrhosis), 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 N-desalkyl quetiapine 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. In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. N-desalkyl quetiapine 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 N-desalkyl quetiapine) 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 medicinal products...
will result in clinically significant inhibition of cytochrome P450-mediated metabolism of the other drug.

**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 cynomologus 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**

*Intragranular*
- Calcium hydrogen phosphate (Dihydrate),
- Lactose monohydrate,
- Microcrystalline cellulose,
- Povidone (PVP K30),

*Extragranular*
- Sodium starch glycollate (Type A),
- Magnesium stearate,

*Film coating material composition*
- Opadry OY-S-58910 White containing:
  - Hypromellose 5cP (E464)
  - Titanium dioxide (E171)
  - Macrogol /PEG 400
  - Talc (E553b)
6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
This medicinal product does not require any special storage condition.

6.5 Nature and contents of container
Blister pack of PVC/PE/PVdC/Al
Or
Blister pack of PVC/ACLAR
Pack sizes: 20, 60 and 30

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

Any unused product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORITY
Ranbaxy (UK) Ltd.,
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

8 MARKETING AUTHORITY NUMBER(S)
PL 14894/0543

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY
17/08/2010

10 DATE OF REVISION OF THE TEXT
17/08/2010

1 NAME OF THE MEDICINAL PRODUCT
Quetiapine 200mg Film-coated tablets.
2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 200mg quetiapine (as fumarate)
This tablet also contains Lactose monohydrate.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film Coated Tablet

White coloured, round tablets debossed with ‘Q5’ on one side and plain 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 can be administered with or without food.

Adults
For the treatment of schizophrenia: Quetiapine should be administered twice daily. 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 therapy to mood stabilizers, 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. 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, the 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 should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on quetiapine 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**
Dosage 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 dosing 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
Hypersensitivity to the active substance or to any of the excipients of this product.
Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIVprotease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated. (See also section 4.5).

### 4.4 Special warnings and precautions for use
**Children and adolescents (10 to 17 years of age)**
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. Clinical trials have shown that in addition to the known safety profile identified in adults (see section 4.8), 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).

**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 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.

**QT Prolongation**
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. 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).

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.

Extrapyramidal symptoms
In placebo controlled clinical trials 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
As with other antipsychotics, there is a potential for quetiapine to cause tardive dyskinesia after long-term treatment. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered.

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

Severe neutropenia
Severe neutropenia (neutrophil count <0.5 x 10⁹/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 is no apparent dose relationship.
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 10⁹/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 x 10⁹/L). (See Section 4.8).

Acute withdrawal reactions
Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhea, 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).

**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 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).

**Elderly patients with dementia-related psychosis**
Quetiapine is not approved for the treatment of dementia-related psychosis. An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo-controlled 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 risk factors for stroke.

**Hepatic effects**
If jaundice develops, quetiapine should be discontinued.

**Lipids**
Increases in triglycerides and cholesterol have been observed in clinical trials with quetiapine (see Section 4.8 Undesirable effects). Lipid increases should be managed as clinically appropriate.

**Lactose**
This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Additional information**
Quetipaine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 and 5.1). 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 QUETIAPINE should be used with caution in combination with other centrally acting drugs and alcohol.

The pharmacokinetics of lithium was 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 (quetiapine fumarate). Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.

The pharmacokinetics of quetiapine was 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.

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 (as 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, and hence, in each patient, consideration for a higher dose of quetiapine, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of quetiapine is 750mg/day for the treatment of schizophrenia and 800mg/day for the treatment of manic episodes associated with bipolar disorder. Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit risk assessment for an individual patient. Co-administration of quetiapine with another microsomal enzyme inducer, phenytoin, also caused increases in the clearance of quetiapine. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and phenytoin and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc.). The dose of quetiapine may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. The pharmacokinetics of quetiapine was not altered following co-administration with cimetidine, a known P450 enzyme inhibitor. The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor). However, caution is recommended when quetiapine is co-administered with potent
CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors). (See also Section 4.4 Special Warnings & Special Precautions for Use and Section 5.2 Pharmacokinetics.) Caution should be exercised when quetiapine is used concomitantly with agents 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 harmlessness 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.

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. 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 are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension, and dyspepsia.

As with other antipsychotics, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with quetiapine.

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

MHRA PAR; QUETIAPINE 25MG, 100MG, 150MG, 200MG AND 300MG FILM-COATED TABLETS, PL 14894/0540 and PL 14894/0542-45
<table>
<thead>
<tr>
<th>Disorder Type</th>
<th>Severity</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine disorders</strong></td>
<td>Common</td>
<td>Hyperprolactinaemia&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Diabetes mellitus&lt;sup&gt;1,5,6&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Metabolism and nutritional disorders</strong></td>
<td>Common</td>
<td>Increased appetite</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Diabetes mellitus&lt;sup&gt;1,5,6&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>Common</td>
<td>Abnormal dreams and nightmares</td>
</tr>
<tr>
<td></td>
<td>Very common</td>
<td>Dizziness&lt;sup&gt;4,17&lt;/sup&gt;, Somnolence&lt;sup&gt;2,17&lt;/sup&gt;, Headache</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Seizure&lt;sup&gt;1&lt;/sup&gt;, Restless legs syndrome,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dysarthria, Tardive dyskinesia&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Very common</td>
<td>Dizziness&lt;sup&gt;4,17&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Somnolence&lt;sup&gt;2,17&lt;/sup&gt;, Headache</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Syncope&lt;sup&gt;4,7&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Extrapiramidal symptoms&lt;sup&gt;1,13&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seizure&lt;sup&gt;1&lt;/sup&gt;, Restless legs syndrome,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dysarthria, Tardive dyskinesia&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>Common</td>
<td>Tachycardia&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td>Common</td>
<td>Vision blurred</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>Common</td>
<td>Orthostatic hypotension&lt;sup&gt;4,17&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Respiratory thoracic and mediastinal disorder</strong></td>
<td>Common</td>
<td>Rhinitis</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorder</strong></td>
<td>Very</td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Constipation, dyspepsia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Dysphagia&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Hepato-biliary disorders</strong></td>
<td>Rare</td>
<td>Jaundice&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Hepatitis&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Very rare</td>
<td>Angioedema&lt;sup&gt;6&lt;/sup&gt;, Stevens-Johnson syndrome&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
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 (predominately LDL cholesterol)\(^{12}\), 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\(^{15}\)

(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 quetiapine.
(3) Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine.
(4) As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. (See section 4.4Special 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 \(\geq 7.0\)mmol/L or a non fasting blood glucose \(\geq 11.1\)mmol/L on at least one occasion.
(8) An increase in the rate of dysphagia with quetiapine 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.
(10) The following withdrawal symptoms have been observed most frequently in acute placebocontrolled, 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 (≥2.258mmol/L) on at least one occasion.
(12) Cholesterol ≥240mg/dL (≥6.2064mmol/L) on at least one occasion. An increase in LDL cholesterol of ≥30mg/dL (≥0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7mg/dL (1.07mmol/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): >20μg/L (>869.56pmol/L) males; >30μg/L (>1304.34pmol/L) females at any time.
(17) May lead to falls.
(18) HDL cholesterol: <40 mg/dL (1.025mmol/L) males; <50 mg/dL (1.282mmol/L) females at any time.

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

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 shortterm, 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 adolescents 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 prolactin¹, increases in blood pressure²

Nervous system disorders

Very common  Extrapyramidal symptoms³

General disorders and administration site conditions

Common  Irritability⁴

1. Prolactin levels (patients < 18 years of age): >20 ug/L (>869.56 pmol/L) males; >26 ug/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 ug/L.
2. Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20mmHg 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 5.1
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 postmarketing 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 active substance's known pharmacological effects, 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 Ssection 4.4).

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: N05A H04

Mechanism of action

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin (5HT₂) and dopamine D₁ and D₂ receptors. Quetiapine exhibits a higher affinity for serotonin (5HT₂) receptors in the brain than it does for dopamine D₁ and D₂ receptors in the brain. Additionally, N-desalkyl quetiapine has high affinity for norepinephrine transporter (NET). Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic α₁ receptors, with a lower affinity at adrenergic α₂-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 depolarization blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurons 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 antidepressant 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 antidepressant 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 totaling 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 0.73% in placebo-treated patients.
109/L was 0.21% in patients treated with quetiapine and 0% in placebo treated patients and the incidence ≥0.5 - <1.0 X 109/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 sections 4.4 and 4.8).

**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 N-desalkyl quetiapine are 35% of that observed for quetiapine. The elimination half-lives of quetiapine and N-desalkyl quetiapine 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 N-desalkyl quetiapine 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) and in subjects with hepatic impairment (stable alcoholic cirrhosis), 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 N-desalkyl quetiapine 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.

*In vitro* investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. N-desalkyl quetiapine 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 N-desalkyl quetiapine) 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 medicinal products will result in clinically significant inhibition of cytochrome P450-mediated metabolism of the other drug.

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 cynomologus 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

Intragranular
Calcium hydrogen phosphate (Dihydrate),
Lactose monohydrate,
Microcrystalline cellulose,
Povidone (PVP K30),
**Extrgranular**
Sodium starch glycollate (Type A),
Magnesium stearate,

**Film coating material composition**
Opadry OY-S-58910 White containing:
Hypromellose 5cP (E464)
Titanium dioxide (E171)
Macrogol /PEG 400
Talc (E553b)

6.2 **Incompatibilities**
Not applicable

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
This medicinal product does not require any special storage condition.

6.5 **Nature and contents of container**
Blister pack of PVC/PE/PVdC/Al
Or
Blister pack of PVC/ACLAR
Pack sizes: 1, 10, 60, 20, 30, 50, 90 and 100 tablets

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements

Any unused product or waste material should be disposed of in accordance with local requirements

7 **MARKETING AUTHORISATION HOLDER**
Ranbaxy (UK) Ltd.,
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 14894/0544

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
17/08/2010
10 DATE OF REVISION OF THE TEXT
17/08/2010

1 NAME OF THE MEDICINAL PRODUCT
Quetiapine 300mg Film-coated tablets.

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

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film Coated Tablet

White coloured, capsule shaped tablets debossed with ‘Q6’ on one side and plain 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 can be administered with or without food.

Adults
For the treatment of schizophrenia: Quetiapine should be administered twice daily. 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 therapy to mood stabilizers, 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
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. 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, the 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 should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on Quetiapine 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
Dosage 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 dosing 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**  
Hypersensitivity to the active substance or to any of the excipients 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).

4.4 **Special warnings and precautions for use**  
**Children and adolescents (10 to 17 years of age)**  
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. Clinical trials have shown that in addition to the known safety profile identified in adults (see section 4.8), 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).

**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 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.

**QT Prolongation**
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. 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).

**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.

**Extrapyramidal symptoms**
In placebo controlled clinical trials, 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).

**Tardive dyskinesia**
As with other antipsychotics, there is a potential for quetiapine to cause tardive dyskinesia after long-term treatment. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered.

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

**Severe neutropenia**
Severe neutropenia (neutrophil count <0.5 $\times$ $10^9/L$) 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 is no apparent dose relationship. 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 4.8).

**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).

**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 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).

**Elderly patients with dementia related psychosis**
Quetiapine is not approved for the treatment of dementia-related psychosis. An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo-controlled 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 risk factors for stroke.

**Hepatic effects**
If jaundice develops, quetiapine should be discontinued.

**Lipids**
Increases in triglycerides and cholesterol have been observed in clinical trials with quetiapine (see Section 4.8 Undesirable effects). Lipid increases should be managed as clinically appropriate.
**Lactose**

This medicinal product contains lactose monohydrate. 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 or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 and 5.1). 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, Quetiapine should be used with caution in combination with other centrally acting drugs and alcohol.

The pharmacokinetics of lithium was 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 (quetiapine fumarate). Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.

The pharmacokinetics of quetiapine was 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.

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 (as 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, and hence, in each patient, consideration for a higher dose of quetiapine, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of quetiapine is 750mg/day for the treatment of schizophrenia and 800mg/day for the treatment of manic episodes associated with bipolar disorder. Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit risk assessment for an individual patient. Co-administration of quetiapine with another microsomal enzyme inducer, phenytoin, also caused increases in the clearance of quetiapine. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and phenytoin and other hepatic enzyme inducers (e.g. barbiturates, rifampicin
etc.). The dose of quetiapine may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. The pharmacokinetics of quetiapine was not altered following co-administration with cimetidine, a known P450 enzyme inhibitor. The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor). However, caution is recommended when quetiapine is co-administered with potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors). (See also Section 4.4 Special Warnings & Special Precautions for Use and Section 5.2 Pharmacokinetics.)

Caution should be exercised when quetiapine is used concomitantly with agents 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.

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. 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 are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension, and dyspepsia.

As with other antipsychotics, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with Quetiapine.

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
Uncommon Extrapyramidal symptoms, Seizure, Restless legs syndrome, Dysarthria, Tardive dyskinesia

Cardiac disorders
Common Tachycardia

Eye disorders
Common Vision blurred

Vascular disorders
Common Orthostatic hypotension

Respiratory thoracic and mediastinal disorder
Common Rhinitis

Gastrointestinal disorder
Very 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 (predominately LDL 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

(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 quetiapine.
(3) Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine.
(4) As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine 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 ≥7.0mmol/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 quetiapine 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.
(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 (≥2.258mmol/L) on at least one occasion.
(12) Cholesterol ≥240mg/dL (≥6.2064mmol/L) on at least one occasion. An increase in LDL cholesterol of ≥30mg/dL (>0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7mg/dL (>1.07mmol/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 (>869.56pmol/L) males; >30 μg/L (>1304.34pmol/L) females at any time.
(17) May lead to falls.
(18) HDL cholesterol: <40 mg/dL (1.025mmol/L) males; <50 mg/dL (1.282mmol/L) females at any time.

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

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 adolescents 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 ug/L (>869.56 pmol/L) males; >26 ug/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 ug/L.

2. Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20mmHg 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 5.1

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 postmarketing 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 drug's known pharmacological effects, 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).

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: N05A H04

Mechanism of action
Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin (5HT₂) and dopamine D₁ and D₂ receptors. Quetiapine exhibits a higher affinity for serotonin (5HT₂) receptors in the brain than it does for dopamine D₁ and D₂ receptors in the brain. Additionally, N-desalkyl quetiapine has high affinity for norepinephrine transporter (NET). Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic α₁ receptors, with a lower affinity at adrenergic α₂-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 depolarization blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurons following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naïve 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 antidepressant 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 antidepressant 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 totaling 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 sections 4.4 and 4.8).

**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 N-desalkyl quetiapine are 35% of that observed for quetiapine. The elimination half-lives of quetiapine and N-desalkyl quetiapine 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 N-desalkyl quetiapine 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) and in subjects with hepatic impairment (stable alcoholic cirrhosis), 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 N-desalkyl quetiapine 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.

*In vitro* investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. N-desalkyl quetiapine 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 N-desalkyl quetiapine) 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.

**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 cynomologus 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

*Intragranular*
Calcium hydrogen phosphate (Dihydrate),
Lactose monohydrate,
Microcrystalline cellulose,
Povidone (PVP K30),

*Extragranular*
Sodium starch glycollate (Type A),
Magnesium stearate,

*Film coating material composition*
Opadry OY-S-58910 White containing:
Hypromellose 5cP (E464)
Titanium dioxide (E171)
Macrogol /PEG 400
Talc (E553b)

6.2 **Incompatibilities**
Not applicable

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
This medicinal product does not require any special storage condition.

6.5 **Nature and contents of container**
Blister pack of PVC/PE/PVdC/Al
Or
Blister pack of PVC/ACLAR
Pack sizes: 6, 10, 20, 30, 50, 60 and 100

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements

Any unused product or waste material should be disposed of in accordance with local requirements

7 **MARKETING AUTHORISATION HOLDER**
Ranbaxy (UK) Ltd.,
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 14894/0545
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17/08/2010

10 DATE OF REVISION OF THE TEXT
17/08/2010
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Quetiapine 25/100/150/200/300 mg
Film-coated tablets
(Quetiapine)

In this leaflet:
1. What Quetiapine tablets are and what are they used for
2. Before you take Quetiapine tablets
3. How to take Quetiapine tablets
4. Possible side effects
5. How to Store Quetiapine tablets
6. Further Information.

1. What Quetiapine Tablets are and what are they used for

• Quetiapine tablets belong to a group of medicines
called antipsychotics, which help to control the
symptoms of a mental illness called schizophrenia.
The symptoms include delusions (having strange or
unusual thoughts), hallucinations (seeing or hearing
things that are not there), experiencing unusual
behaviour, which can be aggressive and becoming
withdrawn and subdued.

• Quetiapine tablets may be used in the treatment of
manic episodes. These episodes cause periods of
excessive cheerfulness and increased activity.
People with this condition may become unusually
irritable, need less sleep than normal and have
quickly changing thoughts. This is known as bipolar
mania.

• Quetiapine tablets may also be used in the treatment of
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 known as bipolar depression.

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

2. Before you take Quetiapine tablets

Taking other medicines

Please tell your doctor or pharmacist if you are taking or
have recently taken any other medicines, including
herbal medications, natural products and medicines
obtained without a prescription.

Tell your doctor if you are taking any of the following:
• medicines for anxiety, depression or mental illness,
• carbamazepine or phenytoin for epilepsy
• medicine to treat an abnormal heart rhythm
• medicine which may affect the level of salts
(potassium, magnesium) in your blood.
• rifampicin (for tuberculosis)
• barbiturates (for difficulty sleeping)
• thioridazine (another anti-psychotic medicine)

Some medicines can cause quetiapine to be removed
from your body more quickly than normal and, therefore,
your treatment may not work as well as it should.

Taking Quetiapine tablets with food and drink

This medicine can be taken with or without food.
Alcohol should be taken with caution whilst taking
Quetiapine tablets as the combined effect of quetiapine
and alcohol can make you feel sleepy.

Pregnancy and breast-feeding

The safety and efficacy of taking quetiapine during
pregnancy or while breast-feeding have not been
confirmed. Talk to your doctor if you are pregnant, trying
to become pregnant or are breast-feeding.
Ask your doctor or pharmacist for advice before taking
any medicine.

Driving and using machines

Quetiapine tablets may make you feel sleepy. You
should not drive or use machinery until you know how
these tablets affect you.

Important information about some of the
ingredients of Quetiapine Tablets

This medicine contains lactose. If you have been told by
your doctor that you have an intolerance to some
sugars, speak to your doctor before taking this
medicine.

3. How To Take Quetiapine Tablets

Always take quetiapine tablets exactly as your doctor
has told you. Do not take more than the doctor told you
to. Check the label carefully for how much to take and

MHRA PAR; QUETIAPINE 25MG, 100MG, 150MG, 200MG AND 300MG FILM-COATED TABLETS, PL 14894/0540 and PL 14894/0542-45

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2. Before you take Quetiapine Tablets

Do not take Quetiapine tablets if:
- You are allergic (hypersensitive) to quetiapine or any of the other ingredients. (See section 6: Further information) Quetiapine tablets (An allergic reaction may include rash, itching, swelling of lips, or hands/feet, or breathing difficulties)
- You are taking any of the following medicines:
  - nelfinavir (for depression)
  - azole medicines such as iraconazole, ketoconazole (for fungal infections)
  - antibiotics such as erythromycin or clarithromycin (medicine for infection)
  - protease inhibitors like nelfinavir (for HIV infection)

Do not take quetiapine if the above applies to you. Talk to your doctor or pharmacist if you are not sure whether you can take quetiapine tablets.

Take special care with Quetiapine tablets

Quetiapine should not be taken by elderly people with dementia (loss of brain function). The group of medicines that quetiapine belongs to may increase the risk of stroke in elderly people with dementia.

Before you take your medicine, tell your doctor if you:
- suffer from low blood pressure
- suffer from a heart condition, abnormal heart rhythm, or disease of the heart or blood vessels
- have ever had a seizure or fit
- have problems with your liver
- suffer from diabetes or have a risk for getting diabetes.

If you do your doctor may check your blood sugar levels while you are taking this medicine.
- have ever had a stroke
- have ever suffered from a low white cell count.

Tell your doctor if you feel very drowsy or have a strong desire for sleep, while on treatment with quetiapine.

If you experience a faster heartbeat, increased breathing, muscle stiffness and/or fever or involuntary movements of the face, body, arms or legs, after taking your tablets, tell your doctor at once.

Thoughts of suicide and worsening of your depression or anxiety disorder

If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, 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 have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

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 or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

How often to take. Your pharmacist or doctor can help if you are not sure.

Dosage

The starting dose will be decided by your doctor and may gradually increase if your illness and needs. After this the dose will usually be between 150 mg and 800 mg each day.

Adults

If you are suffering from schizophrenia:
The usual starting dose is 50 mg (2 tablets of 25 mg). You will take an increasing number of tablets for the first 4 days of treatment. From day 4 onwards the dose may be increased further, depending on how you respond to the treatment. Your doctor will tell you how many tablets you should take each day which is usually 50 mg on the first day, 100 mg on the second day, 200 mg on the third day and 300 mg on the fourth day.

After that, your doctor will adjust your dose according to your needs, within the range of 150 to 750 mg a day.

If you are suffering from manic episodes associated with bipolar disorder:
The usual starting dose is 100 mg on the first day, 200 mg on the second day, 300 mg on the third day and 400 mg on the fourth day. From day 4 onwards the dose may be increased further, depending on how you respond to the treatment. Your doctor will tell you how many tablets you should take each day. The maximum daily dose is 600 mg a day.

If you are suffering from depressive episodes in bipolar disorder:
The usual starting dose is 50 mg on the first day, 100 mg on the second day, 200 mg on the third day and 300 mg on the fourth day. The recommended daily dose is 300 mg. After that, your doctor will adjust your dose according to your needs.

For preventing your symptoms from returning in bipolar disorder:

Your doctor may continue to give you the same dose of quetiapine as given earlier for treating bipolar disorder. The dose may then be adjusted depending on your response and tolerance within the range of 300 mg to 600 mg a day.

Your doctor will advise the lowest effective dose for maintenance therapy.

Method and route of administration

You will take your tablets twice a day for the treatement of bipolar mania or schizophrenia. You will take your tablets once a day, at bedtime, for the treatement of bipolar depression.

For prevention of recurrence of manic, depressive and mixed episodes in bipolar disorder you will take your tablets twice a day. The tablets should be swallowed with water and can be taken with or without food.

Liver problems

Your doctor may give you a lower dose if you have liver disease.

Kidney problems

Dosage adjustment is not necessary in patients with kidney problems.

Elderly patients

Your doctor may give you a lower dose if you are elderly.
Children and adolescents below 18 years should not take this medicine.

If you take more Quetiapine tablets than you should
Signs and symptoms in the event of an overdose include drowsiness and sedation, rapid heartbeat and low blood pressure.
Contact your doctor or nearest hospital casualty department immediately. Take the container and any remaining tablets with you.

If you forget to take Quetiapine tablets
If you forget to take a dose, take that dose as soon as you remember. However, if it is nearly time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take a double dose to make up for forgotten doses.

If you stop taking Quetiapine tablets
Do not suddenly stop taking this medicine without talking to your doctor first, as you might experience withdrawal symptoms such as feeling sick, being sick, headache, diarrhoea, irritability, dizziness and being unable to sleep. 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 and contact a doctor or go to the nearest hospital immediately, as you may need urgent medical attention.

Side effects that are very rare (affects less than 1 in 10,000 people)
- Allergic reactions that may include swelling of the skin and swelling around the mouth.
- Severe allergic reaction that may include difficulty in breathing, dizziness and collapse.
- Serious illness with blistering of the skin, mouth, eyes and genitals.

Side effects that are rare (affects less than 1 in 1,000 people)
- Long lasting sore throat or mouth ulcers, faster breathing, sweating, fever, stiff muscles, feeling very sleepy or faint.

Side effects that are uncommon (affects less than 1 in 100 people)
- Uncontrollable movements, mainly of your face or tongue (tardive dyskinesia).

swelling of the breasts and unexpectedly produce breast milk.
Your doctor may ask you to have blood tests from time to time.

The side effects described above for adults apply for children and adolescents as well. However, the following side effects occur in a higher frequency category in children and adolescents patients (10-17 years of age) as compared to adult population or that have not been identified in adult population.

Side effects that are very common (affects more than 1 in 10 people)
- Increased appetite
- Increased in blood pressure
- Abnormal muscle movements (feeling restless or muscle stiffness without pain, shaking, difficulty starting muscle movements)

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

5. How to Store Quetiapine Tablets
- Keep your tablets out of the reach and sight of children.
- Do not take the tablets past the expiry date, which is clearly marked on the pack.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer needed. These measures will help to protect the environment.

6. Further Information

What Quetiapine tablets contain
The active substance in Quetiapine tablets is Quetiapine.
The tablets come in five strengths containing 25 mg, 100 mg, 150 mg, 200 mg and 300 mg of quetiapine (as fumarate).

Each tablet also contains several inactive ingredients. These are: calcium hydrogen phosphate, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, Macrogol 400, povidone (PVP K30), sodium starch glycollate (type A), and titanium dioxide (E 171). Talc is present only in 100mg, 150mg, 200mg and 300mg. The 25 mg also contain iron oxide (E 172).

What Quetiapine tablets look like and contents of the pack
Each strength of Quetiapine has a different
**Others**

Side effects that are very common (affects more than 1 in 10 people):
- Dizziness (may lead to falls)
- Feeling sleepy (this may go away with time as you continue taking quetiapine (may lead to falls))
- Headache
- Discontinuation symptoms (symptoms which occur when you stop taking quetiapine) include not being able to sleep (insomnia), feeling sick (nausea), headache, diarrhoea, being sick (vomiting), dizziness and irritability. They usually go away 1 week from your last dose.
- Weight gain
- Dry mouth

Side effects that are common (affects less than 1 in 10 people):
- Fainting, rapid heartbeat
- Indigestion
- Weakness (may lead to falls)
- Swollen ankles or legs
- High blood sugar
- Constipation
- Rhinorrhoea (itchy and blocked nose)
- Low blood pressure when standing up which may make you feel dizzy or faint (may lead to falls).
- Blurred vision
- Abnormal muscle movements (feeling restless or muscle stiffness without pain, shaking, difficulty starting muscle movements)
- Abnormal dreams and nightmares
- Feeling more hungry
- Feeling irritable

Side effects that are uncommon (affects less than 1 in 100 people):
- Restless legs, difficulty in swallowing, disturbance in speech
- Fits (seizures)

Side effects that are rare (affects less than 1 in 1,000 people):
- Swelling of the breasts and unexpected production of milk (gallactorrhoea)
- Yellowing of the skin or whites of the eyes caused by liver or blood problems (jaundice)

Side effects that are very rare (affects less than 1 in 10,000 people):
- Worsening of pre-existing diabetes
- Hepatitis (inflammation of the liver)
  If you have to take quetiapine for a long time, it could cause uncontrollable movements, mainly of your face or tongue. Tell your doctor if this happens.

Rarely reports have shown that some antipsychotic medicines may cause life threatening irregular heartbeat, abnormal heart rhythms, a heart attack or sudden unexplained death. Tell your doctor straight away if you suffer from chest pain, palpitations or an irregular heartbeat.

Some side effects are seen only when a blood test is taken which includes increase in the amount of sugar in the blood, increases in certain fat (total cholesterol and triglyceride), decreases in number of certain types of blood cells, decreases in thyroid hormone levels, particularly total T4, and free T4, increase in liver enzymes and increase in the amount of hormone prolactin in the blood. This may cause men and women to have marking/debossing on one side and is plain on the other side.

<table>
<thead>
<tr>
<th>Tablet Size</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg Tablet</td>
<td>The tablets are round, peach coloured, film-coated, round tablets debossed with 'Q1' on one side and plain on the other side.</td>
</tr>
<tr>
<td>100 mg Tablet</td>
<td>The tablets are white coloured, film-coated, round tablets debossed with 'Q3' on one side and plain on the other side.</td>
</tr>
<tr>
<td>150 mg Tablet</td>
<td>The tablets are white coloured, film-coated, round tablets debossed with 'Q4' on one side and plain on the other side.</td>
</tr>
<tr>
<td>200 mg Tablet</td>
<td>The tablets are round are white coloured, film-coated, round tablets debossed with 'Q5' on one side and plain on the other side.</td>
</tr>
<tr>
<td>300 mg Tablet</td>
<td>The tablets are white coloured, film-coated, capsule shaped tablets debossed with 'Q6' on one side and plain on the other side.</td>
</tr>
</tbody>
</table>

The following packs are available:
- 25 mg tablets: 6, 10, 20, 30, 50, 60, 100 tablet pack
- 100 mg tablets: 3, 20, 30, 50, 60, 90, 100 tablet pack
- 150 mg tablets: 20, 30, 90 tablet pack
- 200 mg tablets: 1, 3, 20, 30, 50, 90, 100 tablet pack
- 300 mg tablets (coloured white): 20, 30, 50, 60, 90, 100 tablet pack

Not all packet sizes will be available.

**The marketing authorization holder and manufacturer**

The marketing authorization holder is:
- Ranbaxy (UK) Limited
- Building 4, Chiswick Park, 566 Chiswick High Road, London, W4 5YE
- UK

Quetiapine tablets are manufactured by:
- Ranbaxy Ireland Ltd., Spafield, Cork Road, Cashel, Co. Tipperary, Republic of Ireland
- Basics GmbH, Hemmelrather Weg 201, D-51377 Leverkusen, Germany
- TERAIA SA, 124 Fabricii Str., 400632 Cluj-Napoca, Romania
- Cemeter BRSKft, 2040 Budapest, Vas ut. 2., Hungary

This leaflet was prepared in April 2010.
LABELLING

Blister foil:

Quetiapine
25mg film-coated tablets

Quetiapine
25mg film-coated tablets

Quetiapine
25mg film-coated tablets

Quetiapine
25mg film-coated tablets

Quetiapine
25mg film-coated tablets

Renbaxy (UK) Ltd.,
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

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London, W4 5YE
United Kingdom

Renbaxy (UK) Ltd.,
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom
Blister foil:

Quetiapine 100mg film-coated tablets
Ranbaxy (UK) Ltd.,
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

Quetiapine 100mg film-coated tablets
Ranbaxy (UK) Ltd.,
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

Quetiapine 100mg film-coated tablets
Ranbaxy (UK) Ltd.,
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

Quetiapine 100mg film-coated tablets
Ranbaxy (UK) Ltd.,
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

Quetiapine 100mg film-coated tablets
Ranbaxy (UK) Ltd.,
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom
Blister foil:

Quetiapine 150mg film-coated tablets

Quetiapine 150mg film-coated tablets

Quetiapine 150mg film-coated tablets

Quetiapine 150mg film-coated tablets

Quetiapine 150mg film-coated tablets

Ranbaxy (UK) Ltd.,
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CODE NO. HP14894/0540/04/02

Ranbaxy (UK) Ltd.,
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

CODE No. HP14894/0542/04/02

Ranbaxy (UK) Ltd.,
Building 4, Chiswick Park,
566 Chiswick High Road,
London, W4 5YE
United Kingdom

CODE No. HP14894/0540/04/02
Carton:
Blister foil:

Quetiapine
200mg
film-coated tablets

Quetiapine
200mg
film-coated tablets

Quetiapine
200mg
film-coated tablets

Quetiapine
200mg
film-coated tablets

Quetiapine
200mg
film-coated tablets
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<tr>
<td><strong>300mg</strong></td>
<td>CODE No.: HP702145/UK 05/19/2</td>
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<td><strong>film-coated tablets</strong></td>
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Blister foil: