



# **Public Assessment Report**

## **National Procedure**

**Quetiapine 25 mg film-coated tablets**  
**Quetiapine 100 mg film-coated tablets**  
**Quetiapine 200 mg film-coated tablets**  
**Quetiapine 300 mg film-coated tablets**

**quetiapine (as the fumarate)**

**PL 14251/0169-0170, 0172 & 0173**

**Manx Healthcare Ltd**

## LAY SUMMARY

### Quetiapine 25, 100, 200 and 300 mg film-coated tablets quetiapine (as the fumarate)

This is a summary of the Public Assessment Report (PAR) for Quetiapine 25, 100, 200 and 300 mg film-coated tablets. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Quetiapine tablets in this lay summary for ease of reading.

For practical information about using Quetiapine tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

#### **What are Quetiapine tablets and what are they used for?**

These products are generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised, called Seroquel 25mg, 100mg, 200mg, and 300mg film-coated tablets.

Quetiapine tablets can be used to treat several illnesses, such as:

- Bipolar depression: where patients feel sad, depressed, guilty, lack energy, lose their appetite or can't sleep.
- Mania: where patients may feel very excited, elated, agitated, enthusiastic or hyperactive or have poor judgment including being aggressive or disruptive.
- Schizophrenia: where patients may hear or feel things that are not there, believe things that are not true or feel unusually suspicious, anxious, confused, guilty, tense or depressed.

#### **How do Quetiapine tablets work?**

Quetiapine tablets contains a substance called quetiapine. This belongs to a group of medicines called antipsychotics. This medicine is thought to work by altering the effect of certain chemicals in the brain, called dopamine, serotonin, noradrenaline and acetylcholine. These chemicals have the effect of changing the behaviour, mood and emotions. Dopamine is the main chemical that these medicines have an effect on.

#### **How are Quetiapine tablets used?**

The pharmaceutical form of these medicines is a film-coated tablet and the route of administration is oral (taken by mouth).

The starting dose will be decided by a doctor. The maintenance dose (daily dose) will depend on the patient's illness and needs but will usually be between 150 mg and 800 mg.

Quetiapine tablets are taken once a day, at bedtime or twice a day, depending on the patient's illness. The tablets should be swallowed whole with a drink of water, with or without food. Grapefruit juice should not be consumed while taking Quetiapine tablets as this can affect the way the medicine works. Patients must not stop taking the tablets even if they feel better, unless their doctor tells them to do so.

The dose in elderly people and in patients with liver problems may be adjusted by a doctor. Quetiapine tablets should not be used by children or adolescents aged under 18 years.

For further information on how Quetiapine tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

### **What benefits of Quetiapine tablets have been shown in studies?**

As Quetiapine tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

### **What are the possible side effects of Quetiapine tablets?**

For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at <https://yellowcard.mhra.gov.uk> or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

As Quetiapine tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

### **Why were Quetiapine tablets approved?**

It was concluded that, Quetiapine tablets has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

### **What measures are being taken to ensure the safe and effective use of Quetiapine tablets?**

As for all newly-authorized medicines, a Risk Management Plan (RMP) has been developed for Quetiapine tablets. The RMP details the important risks of Quetiapine tablets, how these risks can be minimised, any uncertainties about Quetiapine tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Quetiapine tablets:

Summary of safety concerns	
	Extrapyramidal symptoms
	Somnolence
	Weight gain
	Lipid changes (increased cholesterol [including increased LDLs], increased triglycerides and decreased HDLs)
	Hyperglycaemia and diabetes mellitus
	Metabolic risk factors
Summary of safety concerns	
Important potential risks	Potential for off-label use and mis-dosing
Missing information	None

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Quetiapine tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

**Other information about Quetiapine tablets**

Marketing Authorisations for Quetiapine tablets were granted in the United Kingdom (UK) on 03 July 2023.

The full PAR for Quetiapine tablets follows this summary.

This summary was last updated in August 2023.

## TABLE OF CONTENTS

I	INTRODUCTION .....	6
II	QUALITY ASPECTS .....	7
III	NON-CLINICAL ASPECTS .....	8
IV	CLINICAL ASPECTS .....	9
V	USER CONSULTATION.....	10
VI	OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION .....	10
	TABLE OF CONTENT OF THE PAR UPDATE .....	16

## I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Quetiapine 25, 100, 200 and 300 mg film-coated tablets (PL 14251/0169-0170, 0172 & 0173) could be approved.

The products are approved for the following indications:

- treatment of schizophrenia.
- treatment of bipolar disorder:
  - For the treatment of moderate to severe manic episodes in bipolar disorder
  - For the treatment of major depressive episodes in bipolar disorder
  - For the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment.

The active substance, quetiapine, is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin (5HT<sub>2</sub>) and dopamine D<sub>1</sub>- and D<sub>2</sub>- receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT<sub>2</sub> relative to D<sub>2</sub>- receptors which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of quetiapine compared to typical antipsychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic alpha<sub>1</sub> receptors and moderate affinity at adrenergic alpha<sub>2</sub> receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity at several muscarinic receptors, which may explain anti-cholinergic (muscarinic) effects. Inhibition of NET and partial agonist action at 5HT<sub>1A</sub> sites by norquetiapine may contribute to quetiapine therapeutic efficacy as an antidepressant.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Seroquel 25mg, 100mg, 200mg, and 300mg film-coated tablets that has been licensed for suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

With the exception of the bioequivalence study submitted, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing Authorisations for Quetiapine tablets were granted in the United Kingdom (UK) on 03 July 2023.

## II QUALITY ASPECTS

### II.1 Introduction

The active substance is quetiapine. One film-coated tablet contains 25 mg, 100 mg, 200 mg or 300 mg of quetiapine (as the fumarate).

In addition to quetiapine (as the fumarate), these products also contain the excipients povidone K30, microcrystalline cellulose, calcium hydrogen phosphate dihydrate, sodium starch glycolate type C, silica colloidal anhydrous and magnesium stearate.

The film coating consists of hypromellose 6 cP (2910) (E464), titanium dioxide (E171), lactose monohydrate, macrogol 3350 and triacetin. The 25 mg tablet also contains iron oxide yellow and iron oxide red (E172) and the 100 mg tablet contains iron oxide yellow (E172).

The finished products are packaged in PVC/aluminium blisters. The 25 mg strength is available in a pack size of 30 or 60 film-coated tablets and the 100, 200 and 300 mg strengths are available in a pack size of 60 or 90 film-coated tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

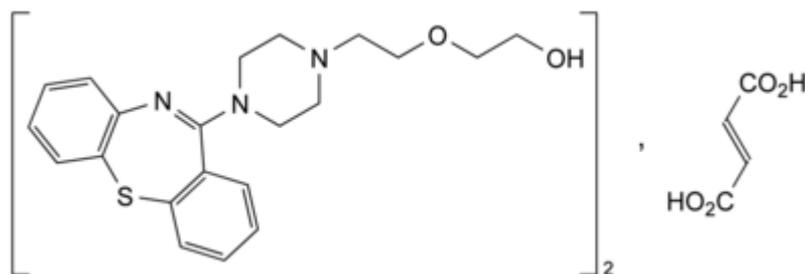
### II.2 ACTIVE SUBSTANCE

**rINN:** quetiapine (as the fumarate)

**Chemical Name:** Bis[2-[2-[4-(dibenzo[*b,f*][1,4]thiazepin-11-yl)piperazin-1-yl]ethoxy]ethanol] (2*E*)-but-2-enedioate

**Molecular Formula:** C<sub>46</sub>H<sub>54</sub>N<sub>6</sub>O<sub>8</sub>S<sub>2</sub>

**Chemical Structure:**



**Molecular Weight:** 883

**Appearance:** White or almost white powder

**Solubility:** Slightly soluble in water, in anhydrous ethanol and in methanol.

Quetiapine (as the fumarate) is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting suitable retest period when stored in the proposed packaging.

## II.3 DRUG PRODUCTS

### Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

### Manufacture of the products

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

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

### Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

### Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with no special storage conditions is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

## II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of marketing authorisations was recommended.

## III NON-CLINICAL ASPECTS

### III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of quetiapine (as the fumarate) are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

**III.2 Pharmacology**

No new pharmacology data were provided, and none were required for these applications.

**III.3 Pharmacokinetics**

No new pharmacokinetic data were provided, and none were required for these applications.

**III.4 Toxicology**

No new toxicology data were provided, and none were required for these applications.

**III.5 Ecotoxicity/Environmental Risk Assessment**

Suitable justification was provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of an already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

**III.6 Discussion on the non-clinical aspects**

The grant of marketing authorisations was recommended.

**IV CLINICAL ASPECTS****IV.1 Introduction**

The clinical pharmacology, efficacy and safety of quetiapine (as the fumarate) are well-known. With the exception of data from a bioequivalence study undertaken (07 ANE-1421 (70213)), no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of the study is, thus, satisfactory.

**IV.2 Pharmacokinetics**

In support of the application, the applicant submitted the following:

Study 1: 07 ANE-1421 (70213)

This study was a single centre, bioequivalence, open-label, single-dose, randomised, 2-way crossover study comparing quetiapine 25 mg film-coated tablet (test product) versus Seroquel 25 mg film-coated tablet (reference product) in healthy human subjects under fasting conditions.

A single dose of either the test or reference product was administered after an overnight fast of at least 10 hours, in each study period. Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

<b>Pharmacokinetic parameter</b>	<b>Geometric Mean Ratio Test/Ref</b>	<b>Confidence Intervals</b>	<b>CV%<sup>1</sup></b>
AUC <sub>(0-t)</sub> <sup>2</sup>	96.97%	89.20 - 105.41 %	21.80 %
Cmax	95.83%	84.92 - 108.14 %	31.98 %

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the 25 mg test product and the 25 mg reference product.

As the additional (100, 200 and 300 mg) strengths of the product meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the product strength can be extrapolated to the other strengths.

#### **IV.3 Pharmacodynamics**

No new pharmacodynamic data were submitted for these applications and none were required.

#### **IV.4 Clinical efficacy**

No new efficacy data were submitted with these applications and none were required.

#### **IV.5 Clinical safety**

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

#### **IV.6 Risk Management Plan (RMP)**

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

#### **IV.7 Discussion on the clinical aspects**

The grant of marketing authorisations was recommended for these applications.

### **V USER CONSULTATION**

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to Seroquel film-coated tablets (PL 12619/0112, PL 12619/0113 and PL 12619/0114; Zeneca Limited (subsequently named AstraZeneca UK Limited)) and Quetiapine 150 mg film-coated tablets (PL 14251/0171; Manx Healthcare Limited). The bridging report submitted by the applicant is acceptable.

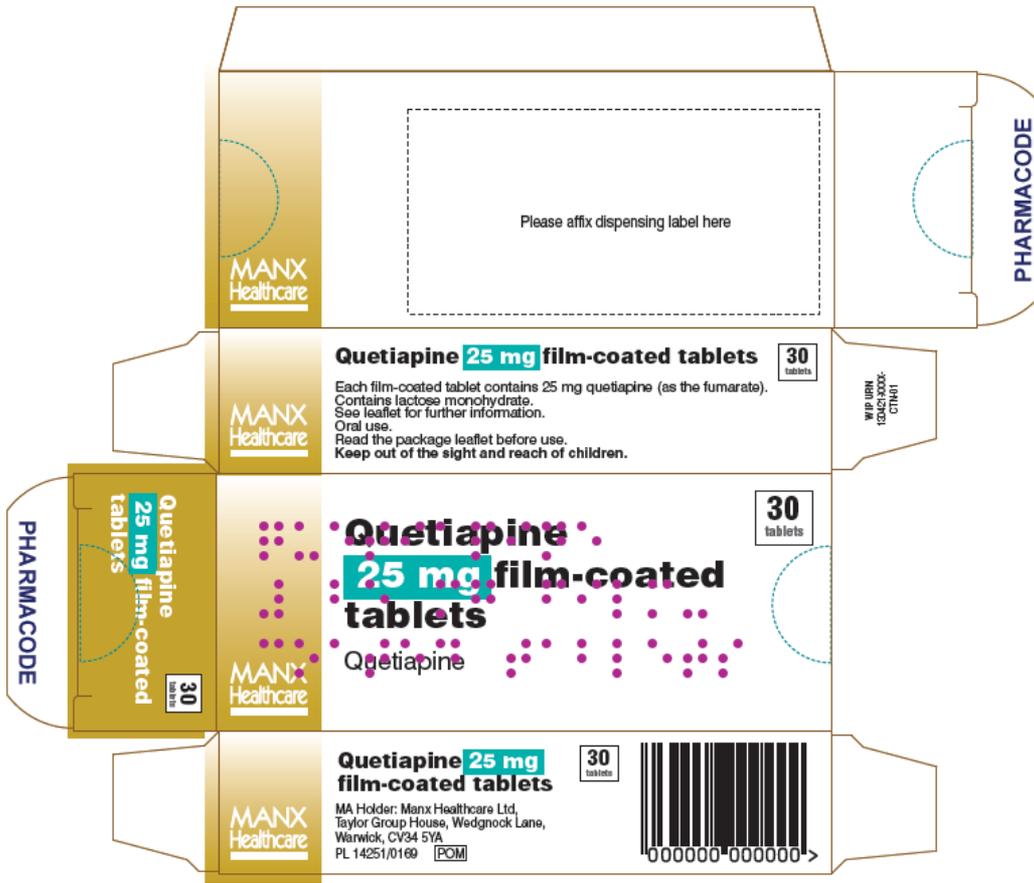
### **VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with quetiapine (as the fumarate) is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.

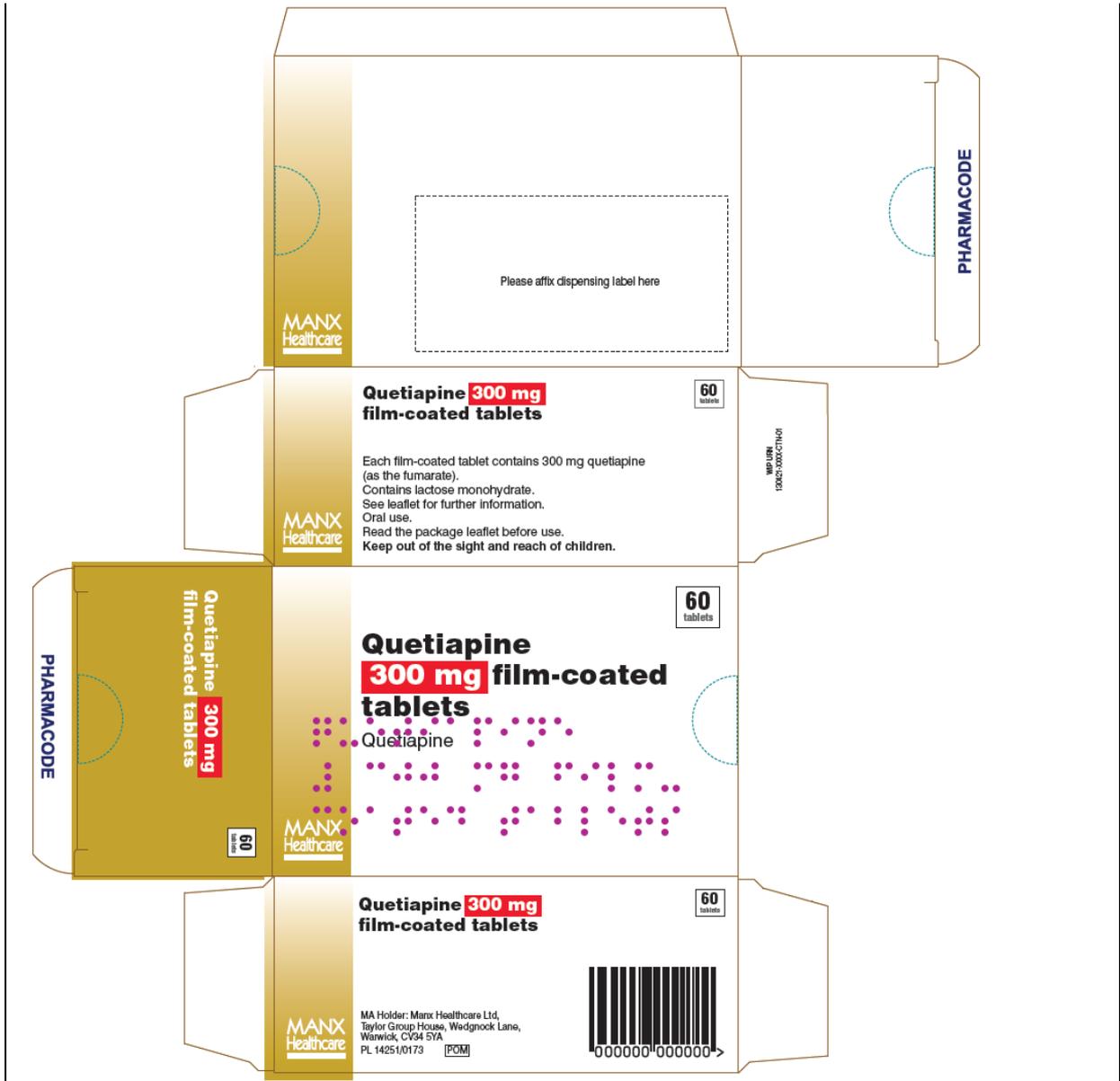


<b>5 mg tablets</b>	<b>Quetiapine 25 mg film-coated tablets</b>	<b>Quetiapine 25 mg film-coated tablets</b>	<b>Quetiapine 25 mg film-coated tablets</b>
Manx Healthcare Ltd	Manx Healthcare Ltd	Manx Healthcare Ltd	Manx Healthcare Ltd
WP URN: 050221-XXXX-FOL-01	WP URN: 050221-XXXX-FOL-01	WP URN: 050221-XXXX-FOL-01	WP URN: 050221-XXXX-FOL-01
<b>5 mg tablets</b>	<b>Quetiapine 25 mg film-coated tablets</b>	<b>Quetiapine 25 mg film-coated tablets</b>	<b>Quetiapine 25 mg film-coated tablets</b>
Manx Healthcare Ltd	Manx Healthcare Ltd	Manx Healthcare Ltd	Manx Healthcare Ltd
WP URN: 050221-XXXX-FOL-01	WP URN: 050221-XXXX-FOL-01	WP URN: 050221-XXXX-FOL-01	WP URN: 050221-XXXX-FOL-01
<b>5 mg tablets</b>	<b>Quetiapine 25 mg film-coated tablets</b>	<b>Quetiapine 25 mg film-coated tablets</b>	<b>Quetiapine 25 mg film-coated tablets</b>
Manx Healthcare Ltd	Manx Healthcare Ltd	Manx Healthcare Ltd	Manx Healthcare Ltd
WP URN: 050221-XXXX-FOL-01	WP URN: 050221-XXXX-FOL-01	WP URN: 050221-XXXX-FOL-01	WP URN: 050221-XXXX-FOL-01
<b>5 mg tablets</b>	<b>Quetiapine 25 mg film-coated tablets</b>	<b>Quetiapine 25 mg film-coated tablets</b>	<b>Quetiapine 25 mg film-coated tablets</b>
Manx Healthcare Ltd	Manx Healthcare Ltd	Manx Healthcare Ltd	Manx Healthcare Ltd
WP URN: 050221-XXXX-FOL-01	WP URN: 050221-XXXX-FOL-01	WP URN: 050221-XXXX-FOL-01	WP URN: 050221-XXXX-FOL-01



<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01	<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01	<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01	<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01
<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01	<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01	<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01	<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01
<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01	<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01	<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01	<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01
<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01	<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01	<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01	<b>Quetiapine 100 mg film-coated tablets</b> Manx Healthcare Ltd WP URN: 050221-XXXX-FOL-01





Coding area	EXP	100 mg tablets	Quetiapine 300 mg film-coated tablets	Quetiapine 300 mg film-coated tablets	Quetiapine 300 mg film-coated tablets	Coding area
		Manx Healthcare Ltd WIP URN: 050221-XXXX-FOL-01				
Coding area	EXP	100 mg tablets	Quetiapine 300 mg film-coated tablets	Quetiapine 300 mg film-coated tablets	Quetiapine 300 mg film-coated tablets	Coding area
		Manx Healthcare Ltd WIP URN: 050221-XXXX-FOL-01				
Coding area	EXP	100 mg tablets	Quetiapine 300 mg film-coated tablets	Quetiapine 300 mg film-coated tablets	Quetiapine 300 mg film-coated tablets	Coding area
		Manx Healthcare Ltd WIP URN: 050221-XXXX-FOL-01				
Coding area	EXP	100 mg tablets	Quetiapine 300 mg film-coated tablets	Quetiapine 300 mg film-coated tablets	Quetiapine 300 mg film-coated tablets	Coding area
		Manx Healthcare Ltd WIP URN: 050221-XXXX-FOL-01				
Coding area	EXP	100 mg tablets	Quetiapine 300 mg film-coated tablets	Quetiapine 300 mg film-coated tablets	Quetiapine 300 mg film-coated tablets	Coding area
		Manx Healthcare Ltd WIP URN: 050221-XXXX-FOL-01				
Coding area	EXP	100 mg tablets	Quetiapine 300 mg film-coated tablets	Quetiapine 300 mg film-coated tablets	Quetiapine 300 mg film-coated tablets	Coding area
		Manx Healthcare Ltd WIP URN: 050221-XXXX-FOL-01				

**TABLE OF CONTENT OF THE PAR UPDATE**

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

<b>Application type</b>	<b>Scope</b>	<b>Product information affected</b>	<b>Date of grant</b>	<b>Outcome</b>	<b>Assessment report attached Y/N</b>