COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Quetiapine Accord 150 mg modified-release tablets
(quetiapine fumarate)

NL/H/4781/005/DC

Date: 2 March 2023

This module reflects the scientific discussion for the approval of Quetiapine Accord 150 mg modified-release tablets. The procedure was finalised in the United Kingdom (UK/H/3524/005/DC). After a transfer in 2019, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Atrolak XL 150 mg prolonged-release tablets

(Quetiapine fumarate)

Procedure No: UK/H/3524/005/DC

UK Licence Number: PL 20075/0446

Accord Healthcare Limited.

LAY SUMMARY

Atrolak XL 150 mg prolonged-release tablets

(quetiapine fumarate, prolonged-release tablet, 150 mg)

This is a summary of the Public Assessment Report (PAR) for Atrolak XL 150 mg prolonged-release tablets (PL 20075/0446; UK/H/3524/005/DC). It explains how Atrolak XL 150 mg prolonged-release tablets 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 Atrolak XL 150 mg prolonged-release tablets.

The product will be referred to as Atrolak XL throughout the remainder of this public assessment report (PAR).

For practical information about using Atrolak XL, patients should read the package leaflet or contact their doctor or pharmacist.

What is Atrolak XL and what is it used for?
Atrolak XL is a 'generic medicine'. This means that Atrolak XL is similar to a 'reference medicine' already authorised in the European Union (EU) called Seroquel XL 150 mg prolonged-release tablets (AstraZeneca UK Ltd, UK).

Atrolak XL can be used to treat several illnesses, such as:

- Schizophrenia: where the patient 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.
- Mania: where the patient may feel very excited, elated, agitated, enthusiastic or hyperactive or have poor judgment including being aggressive or disruptive.
- Bipolar depression and major depressive episodes in major depressive disorder: where the patient feels sad. The patient may find that they feel depressed, feel guilty, lack energy, lose their appetite or can't sleep.

When Atrolak XL is being taken to treat major depressive episodes in major depressive disorder, it will be taken in addition to another drug being used to treat this illness.

The patient's doctor may continue to prescribe Atrolak XL even when they are feeling better.

How does Atrolak XL work?
Atrolak XL contains a substance called quetiapine. This belongs to a group of medicines called anti-psychotics which work on the balance of chemical substances in the patient's brain.

How is Atrolak XL used?
The pharmaceutical form of this medicine is a prolonged-release tablet and the route of administration is oral (by mouth).

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

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

- The patient will take their tablets once a day.
- The patient must not split, chew or crush the tablets.

- Swallow the tablets whole with a drink of water.
- Take the tablets without food (at least one hour before a meal or at bedtime, the patient's doctor will tell them when).
- The patient should not drink grapefruit juice while they are taking Atrolak XL. It can affect the way the medicine works
- The patient should not stop taking their tablets even if they feel better, unless their doctor tells them.

Liver problems
If the patient has liver problems, their doctor may change their dose.

Elderly people
If the patient is elderly, their doctor may change their dose.

Use in children and adolescents
Atrolak XL should not be used by children and adolescents aged under 18 years.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Atrolak XL is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Atrolak XL have been shown in studies?
Because Atrolak XL is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine Seroquel XL 150 mg prolonged-release tablets (AstraZeneca UK Ltd). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Atrolak XL?
Because Atrolak XL is a generic medicine and is bioequivalent to the reference medicine Seroquel XL 150 mg prolonged-release tablets (AstraZeneca UK Ltd), its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Atrolak XL, see section 4 of the package leaflet available on the MHRA website.

Why was Atrolak XL approved?
It was concluded that, in accordance with EU requirements, Atrolak XL has been shown to have comparable quality and to be bioequivalent to Seroquel XL 150 mg prolonged-release tablets (AstraZeneca UK Ltd). Therefore, the MHRA decided that, as for Seroquel XL 150 mg prolonged-release tablets (AstraZeneca UK Ltd); 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 Atrolak XL?
A risk management plan (RMP) has been developed to ensure that Atrolak XL is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Atrolak XL including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Atrolak XL
Agreement for granting a Marketing Authorisation was given on 08 June 2016 by the UK and the following EU member states: Austria, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Lithuania, Latvia, Malta, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia and the Slovak.
A Marketing Authorisation was granted in the UK on 16 June 2016.

The full PAR for Atrolak XL follows this summary.

For more information about treatment with Atrolak XL, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2016.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Accord Healthcare Limited, a marketing authorisation for the medicinal product Atrolak XL (PL 20075/0446; UK/H/3524/005/DC). The product is a prescription-only medicine (POM) indicated for:

- 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

- add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy (see Section 5.1 of the SmPC). Prior to initiating treatment, clinicians should consider the safety profile of Atrolak XL (see Section 4.4 of the SmPC).

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Austria, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Lithuania, Latvia, Malta, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia and the Slovak Republic as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product authorised for not less than 10 years in the EEA is Seroquel 200mg Tablets (PL 17901/0040) which was authorised in the UK to AstraZeneca UK on 31 July 1997. The reference medicinal product for this application is Seroquel XL 150 mg prolonged-release tablets PL 17901/0259 (AstraZeneca UK Ltd) which was first authorised in the UK to AstraZeneca UK Ltd on 12 March 2010.

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 ($5HT_2$) and dopamine D_1- and D_2- receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2- 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 alpha1 receptors and moderate affinity at adrenergic alpha2 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 norepinephrine transporter (NET) and partial agonist action at 5HT1A sites by norquetiapine may contribute to quetiapine prolonged-release tablets therapeutic efficacy as an antidepressant.

Three bioequivalence studies (single-dose studies conducted under fed and fasting conditions and a multiple-dose (steady state) study conducted under fasting conditions) were submitted to support this application. The applicant has stated that the bioequivalence studies were conducted in accordance with the protocol and were compliant with all the requirements regarding the obligations of investigators & all other pertinent requirements of the Schedule Y (amended version, 2013) of CDSCO (Central Drugs Standard Control Organization), Ministry of health and family welfare, Government of India, Ethical guidelines for biomedical research on human participants, ICMR [Indian Council of Medical Research (2006)], ICH (International Conference on Harmonization) E6 (R1) 'Guideline for Good Clinical Practice' 1996 and Declaration of Helsinki (Brazil, 2013).

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that this is a generic medicinal product of an originator product that has been in clinical use for over 10 years.

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

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure on 08 June 2016. After a subsequent national phase, a licence was granted in the UK on 16 June 2016.

II QUALITY ASPECTS

II.1 Introduction

Each prolonged-release tablet contains 150 mg quetiapine (as quetiapine fumarate), as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

Core:

Lactose monohydrate, hypromellose 3550, hypromellose 100, sodium chloride, povidone K-30, microcrystalline cellulose, talc and magnesium stearate.

Coating (opadry white):

Poly(vinyl alcohol), titanium dioxide (E171), macrogol 3350 and talc.

The finished product is packed in to the following presentations and pack sizes:

- White opaque polyvinyl chloride(PVC)/polyvinylidene chloride (PVDC)- aluminium (Alu) blisters or oriented polyamide (OPA)/Alu/PVC-Alu blisters in pack sizes 10, 30, 50, 60, and 100 tablets.
- White, opaque, high-density polyethylene (HDPE) bottles with a white opaque polypropylene child resistant closure with wad having induction sealing liner in pack sizes of 60 and 100 tablets.

Not all pack sizes may be marketed.

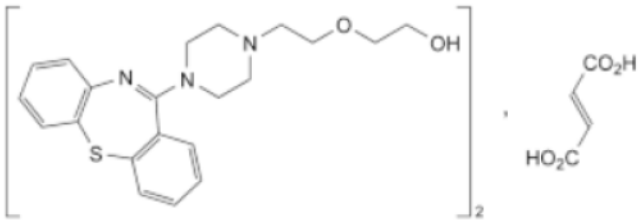
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance

INN: Quetiapine 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.

Structure:



Molecular formula: $C_{46}H_{54}N_6O_8S_2$

Molecular weight: 883 g/mol

Description: White or almost white powder.

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

Quetiapine fumarate is the subject of a European Pharmacopoeia monograph.

Data on the drug substance has been provided using the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability or Active Substance Master File (ASMF) from the suppliers.

For drug substance information presented using the Certificate of Suitability, all aspects of the manufacture, control and retest period (when stored in the proposed packaging) of the quetiapine fumarate, are covered by the EDQM Certificate of Suitability submitted.

For drug substance information presented using the ASMF, synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory certificates of analysis have been provided for all working standards. Batch analyses data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

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

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious prolonged-release tablets containing 150 mg quetiapine (as quetiapine fumarate) per tablet, that are a generic versions of the reference product Seroquel XL 150 mg prolonged-release tablets (AstraZeneca UK Ltd). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in-vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the opadry white film-coating colour which is controlled to a suitable in-house specification. The supplier has confirmed that all the ingredients contained in the opadry white coat meet appropriate regulatory/compendial requirements for their intended use. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

Satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 30 months for the blister packs and bottles with no special storage conditions. The in-use shelf life for the tablets packaged in bottles is 100 days after first opening the bottle.

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

There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of quetiapine 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.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Atrolak XL is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary**.**

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of quetiapine fumarate is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of quetiapine fumarate.

Based on the data provided, Atrolak XL can be considered bioequivalent to Seroquel XL 150 mg prolonged-release tablets (AstraZeneca UK Ltd).

IV.2 Pharmacokinetics

In support of this application, the applicant submitted the following three bioequivalence studies:

STUDY 1

An open label, balanced, randomised, two-treatment, two period, two-sequence, single oral dose, crossover, bioequivalence study of the applicant's test product Atrolak XL 150 mg prolonged-release tablets versus the reference product to Seroquel XL 150 mg prolonged-release tablets (AstraZeneca UK Ltd) in healthy, adult, subjects under fasting conditions.

Following an overnight fast of at least 10 hours, subjects were administered a single dose (1 x 150 mg prolonged-release tablet) of the test or the reference product with 240 mL of water at ambient temperature.

Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. The washout period between the treatment phases was 8 days. The pharmacokinetic results are presented below:

Table: Summary of Pharmacokinetic data for quetiapine:

Parameters	Geometric Least Squares Means			90% Confidence Interval	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%		
lnC_{max}	216.964	230.588	94.1	88.03 - 100.57	100.0
$lnAUC_{0-t}$	3708.433	3832.365	96.8	90.42 - 103.56	100.0
$lnAUC_{0-\infty}$	3803.132	3901.326	97.5	91.12 - 104.29	100.0

AUC_{0-t} area under the plasma concentration-time curve from zero to t hours
AUC0-∞ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration

STUDY 2

An open label, balanced, randomised, two-treatment, two period, two-sequence, single oral dose, crossover, bioequivalence study of the applicant's test product Atrolak XL 150 mg prolonged-release tablets versus the reference product to Seroquel XL 150 mg prolonged-release tablets (AstraZeneca UK Ltd) in healthy, adult, subjects under fed conditions.

Following an overnight fast of at least 10 hours, the subjects were served a high fat and high calorie vegetarian breakfast which was consumed within 30 minutes. Subjects were administered a single dose (1 x 150 mg prolonged-release tablet) of the test or the reference product with 240 mL of water at ambient temperature, 30 minutes after the breakfast was served.

Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below:

Table: Summary of Pharmacokinetic data for quetiapine:

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	284.240	304.598	93.3	86.79 - 100.33	25.1	100.0
$lnAUC_{0-t}$	2728.802	2659.099	102.6	97.33 - 108.20	18.2	100.0
$lnAUC_{0-\infty}$	2757.987	2683.352	102.8	97.47 - 108.38	18.3	100.0

STUDY 3

An open label, two-way crossover, multiple-dose, bioequivalence study of the applicant's test product Atrolak XL 150 mg prolonged-release tablets versus the reference product to Seroquel XL 150 mg prolonged-release tablets (AstraZeneca UK Ltd) in healthy, adult, subjects under fasting conditions.

Subjects were required to fast for at least 10 hours prior to each dose. No food was allowed for at least 5 hours post-dose.

Each treatment was administered with 240 mL of ambient temperature water. No water was permitted for 1.0 hour pre-dose on all dosing days. The treatment included 1 or more tablets at a time, but all tablets were ingested within 1 minute. The study drugs were swallowed whole, not chewed or crushed. The study drugs were administered daily for 5 consecutive days. The actual dosing time was recorded when the first tablet was orally given (or both tablets if they were taken together). Subjects randomly received the test or reference product during days 03 to 07 (period I) or days 08-12 (period II).

The drug administration is summarised in the table below:

Treatment	Day 1	Day 2	Day 3-7	Day 8-12	Day 13	Day 14
1 x Seroquel XL® 50mg prolonged release tablets (Quetiapine Fumarate)	X					X
2 x Seroquel XL® 50mg prolonged release tablets (Quetiapine Fumarate)		X			X	
1 x Quetiapine Fumarate ER Tablets 150mg **OR** 1 x Seroquel® XL 150mg prolonged release tablets quetiapine (as fumarate)			X	X		

Test product T= Quetiapine Fumerate ER Tablets 150mg (Atrolak XL 150 mg prolonged-release tablets, Accord Healthcare Limited)
Reference product R= Seroquel XL 150 mg prolonged-release tablets, quetiapine (as fumarate) [AstraZeneca UK Ltd]
Reference product for titration- Seroquel XL 50 mg prolonged-release tablets, quetiapine (as fumarate) [AstraZeneca UK Ltd].

Blood samples were collected for plasma levels before dosing and up to and including 24 hours post-dose. There was no washout period. The pharmacokinetic results are presented below:

Table: Summary of Pharmacokinetic data for quetiapine:

Parameters	Geometric Least Squares Means			90% Confidence Interval	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%		
$\ln C_{max,ss}$	145.019	164.745	88.0	83.01 - 93.34	100.0
$\ln C_{\tau,ss}$	33.869	30.495	111.1	100.06 - 123.28	96.9
$\ln AUC_{0-\tau,ss}$	1867.916	1900.574	98.3	94.30 - 102.43	100.0

Table: Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD):

Treatment	$AUC_{0-\tau}$ xg/ml/h	$C_{max,ss}$ xg/ml	$C_{\tau,ss}$ xg/ml	$t_{max,ss}$ h
Test	2024.937 ± 830.8206	157.151 ± 65.3974	41.615 ± 26.7164	5.500 (1.000 - 16.000)
Reference	2057.985 ± 852.5328	179.216 ± 76.6143	35.406 ± 19.3378	5.500 (2.000 - 16.000)
*Ratio (90% CI)	98.3 (94.30 - 102.43)	88.0 (83.01 - 93.34)	111.1 (100.06 - 123.28)	

$AUC_{0-\tau}$ Area under the plasma concentration curve during a dosage interval at steady state
$C_{max,ss}$ Maximum plasma concentration at steady state
$C_{\tau,ss}$ Minimum plasma concentration at steady state
$t_{max,ss}$ Time until Cmax,ss is reached

**ln-transformed values*

Conclusion
The 90% confidence intervals of the test/reference ratios for AUC, C_{max} , $AUC_{0-\tau}$, $C_{max,ss}$ and $C_{\tau,ss}$ values for quetiapine (administered as a single dose under fasting and fed conditions and multiple-dose (steady state) under fasting conditions) lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**) and 'Guideline on pharmacokinetic and clinical evaluation of modified release dosage forms' (EMA/CPMP/EWP/280/96 Corr1). Thus, the data support the claim that the applicant's test product Atrolak XL (Accord Healthcare Limited) is bioequivalent to the reference product Seroquel XL 150 mg prolonged-release tablets (AstraZeneca UK Ltd)

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to quetiapine fumarate.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

Important identified risks (s)	• Hyperglycaemia and diabetes • Hypothyroidism • Increased blood pressure in paediatric population • Agranulocytosis • QT prolongation • Metabolic risk factors • Venous thromboembolism • Pancreatitis • Extrapyramidal symptoms • Tardive dyskinesia • Somnolence • Syncope and orthostatic hypotension • Seizure • Neutropenia • Weight gain • Lipid changes (increased cholesterol (including increased LDLs), increased triglycerides, and decreased HDLs) • Hyperprolactinaemia

	• Anaphylactic reaction • Jaundice, hepatitis and increased serum transaminase and gamma-glutamyl transpeptidase (GGT) • Stevens johnson syndrome • Neuroleptic malignant syndrome • Withdrawal (discontinuation) symptoms and neonatal withdrawal • Dysphagia • Intestinal obstruction • Hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Important potential risks	• Safety in elderly patients • Cerebrovascular adverse effects in elderly patients • Cerebrovascular adverse effects in non-elderly patients • Ischaemic heart disease • Aggression/ agitation • Suicide and suicidality • Aspiration pneumonia • Potential for off-label use and misdosing • Torsade de pointes • Increased mortality in elderly demented patients • Abuse and misuse • Accidental injury • Concomitant use of valproic acid
Missing information	• Safety in pregnant or breastfeeding women • Safety in patient on concomitant cardiovascular medications

Summary table of risk minimisation measures:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified risks: Hyperglycaemia and diabetes	Section 4.4 and 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	Education material for healthcare professional will be distributed by MAH.
Important Identified risks:	Section 4.4, 4.8 and 5.1 of Quetiapine Accord SmPC and	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypothyroidism	corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	
Important Identified risks: Increased blood pressure in paediatric population	Section 4.4, 4.8 and 5.1 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified risks: Agranulocytosis	Section 4.4, 4.8 and 5.1 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified risks: QT prolongation	Section 4.4, 4.5, 4.8 and 4.9 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	only status of the product.	
Important Identified risks: Metabolic risk factors	Section 4.4 and 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	Education material for healthcare professional will be distributed by MAH.
Important Identified risks: Venous thromboembolism	Section 4.4 and 4.8 of Quetiapine Accord SmPC has been proposed with information on this safety concern Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified risks: Pancreatitis	Section 4.4 and 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified risks:	Section 4.4, 4.5 4.6, 4.8 and 5.1 of Quetiapine Accord SmPC and	Education material for healthcare professional will be distributed by

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Extrapyramidal symptoms	corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	MAH.
Important Identified risks: Tardive dyskinesia	Section 4.4 and 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified risks: Somnolence	Section 4.4, 4.5, 4.6 and 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	Education material for healthcare professional will be distributed by MAH.
Important Identified risks: Syncope and orthostatic hypotension	Section 4.4, 4.8 and 4.9 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	only status of the product.	
Important Identified risks: Seizure	Section 4.4, 4.8 and 4.9 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified risks: Neutropenia	Section 4.4, 4.5 and 4.8 of Quetiapine Accord SmPC has information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified risks: Weight gain	Section 4.4, 4.5 4.8 and 5.1 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	Education material for healthcare professional will be distributed by MAH.
Important Identified risks: Lipid changes	Section 4.4 and 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information	Education material for healthcare professional will be distributed by MAH.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
(increased cholesterol (including increased LDLs), increased triglycerides, and decreased HDLs)	on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	
Important Identified risks: Hyperprolactinaemia	Section 4.4, 4.6, 4.8 and 5.1 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified risks: Anaphylactic reaction	Section 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified risks: Jaundice, hepatitis and increased serum transaminase and	Section 4.4 and 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
gamma-glutamyl transpeptidase (GGT)	measures including the prescription only status of the product.	
Important Identified risks: Stevens johnson syndrome	Section 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified risks: Neuroleptic malignant syndrome	Section 4.4 and 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified risks: Withdrawal (discontinuation) symptoms and neonatal withdrawal	Section 4.4, 4.6 and 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified risks: Dysphagia	Section 4.4 and 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified risks: Intestinal obstruction	Section 4.4 and 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified risks: Hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Section 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Potential risks: Safety in elderly	Section 4.2 and 4.4 of Quetiapine Accord SmPC and corresponding sections of PIL have information	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
patients	on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	
Important Potential risks: Cerebrovascular adverse effects in elderly patients	Section 4.4 and 5.1 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Potential risks: Cerebrovascular adverse effects in non-elderly patients	Section 4.4 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Potential risks: Ischaemic heart disease	None proposed	None proposed
Important Potential risks: Aggression/	Section 4.6 and 4.9 of Quetiapine Accord SmPC and corresponding sections of PIL have information	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
agitation	on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	
Important Potential risks: Suicide and suicidality	Section 4.4, 4.8 and 5.1 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Potential risks: Aspiration pneumonia	Section 4.4 of Quetiapine Accord SmPC has information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Potential risks: Potential for off-label use and misdosing	Section 4.2 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	Education material for healthcare professional will be distributed by MAH.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Potential risks: Torsade de pointes	Section 4.8 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Potential risks: Increased mortality in elderly demented patients	Section 4.4 and 5.1 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Potential risks: Abuse and misuse	None Proposed, however, as per Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting, dated 05-08 May 2014, signal of "abuse and misuse of quetiapine" needed to further review based on the evidence available in suspected cases and literature.	None proposed
Important Potential risks:	Section 4.4 of Quetiapine Accord SmPC and corresponding sections	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Accidental injury	of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	
Important Potential risks: Concomitant use of valproic acid	Section 4.5 of Quetiapine Accord SmPC has information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Missing information: Safety in pregnant or breastfeeding women	Section 4.6, 4.8 and 5.3 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Missing information: Safety in patient on concomitant cardiovascular medications	Section 4.5 of Quetiapine Accord SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Seroquel XL 150 mg prolonged-release tablets (procedure number: NL/H/0156/006/MR) for the PIL content and Mycophenolic acid 180mg and

360mg gastro-resistant tablets (procedure number: ES/H/0183/001-2/DC) for design, layout and style. The bridging report submitted by the applicant has been found acceptable.

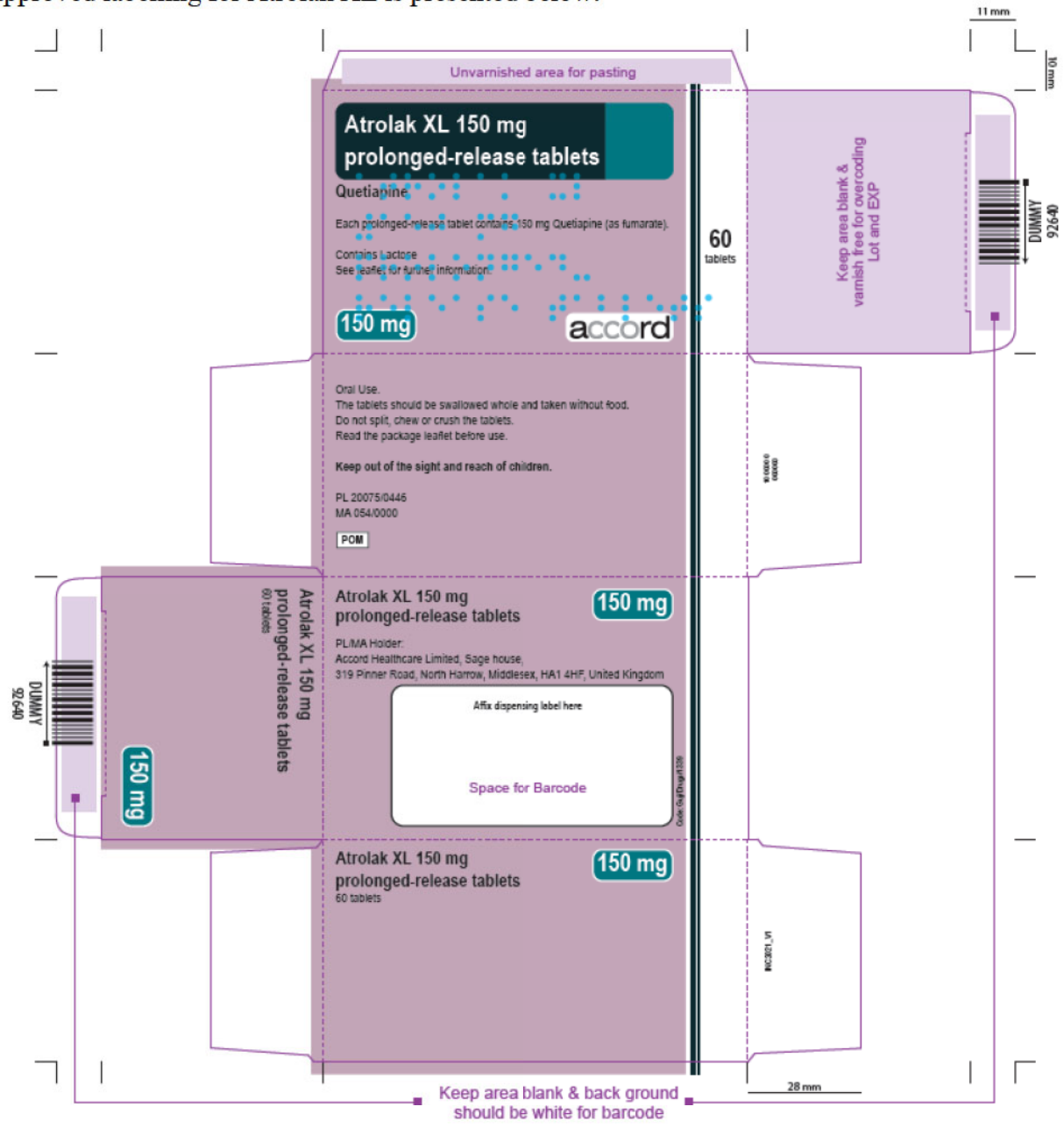
VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with quetiapine fumarate is considered to have demonstrated the therapeutic value of the compound. The product is bioequivalent to the marketed reference product and its risk-benefit balance is considered similar and positive.

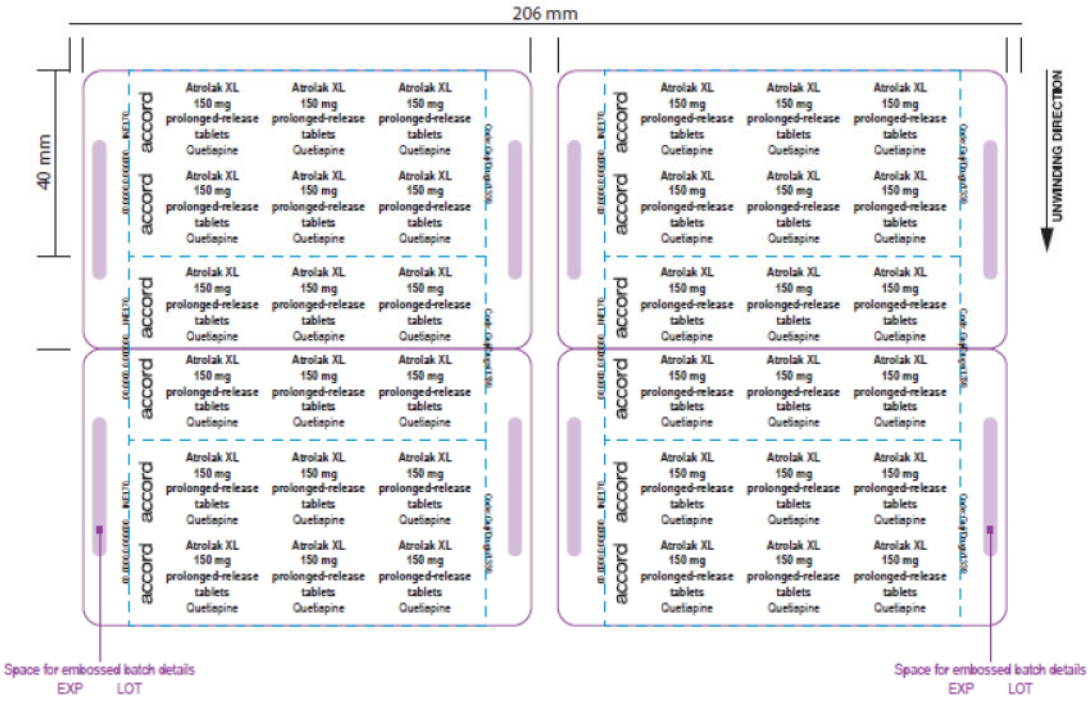
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Atrolak XL is presented below:



Atrolak XL #150 mg prolonged-release tablets


206 mm
40 mm
UNWINDING DIRECTION
Atrolak XL 150 mg prolonged-release tablets Quetiapine
accord
Space for embossed batch details
EXP LOT
Space for embossed batch details
EXP LOT