COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Quetiapine Accord 50 mg modified-release tablets
(quetiapine fumarate)

NL/H/4781/004/DC

Date: 2 March 2023

This module reflects the scientific discussion for the approval of Quetiapine Accord 50 mg modified-release tablets. The procedure was finalised in the United Kingdom (UK/H/3524/004/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.

Public Assessment Report

Decentralised Procedure

Atrolak XL 50 mg prolonged-release Tablets

(Quetiapine fumarate)

UK/H/3524/004/DC

UK licence no: PL 20075/0213

Accord Healthcare Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

On 19th June 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) to Accord Healthcare Limited for the medicinal product Atrolak XL 50 mg prolonged-release Tablets (PL 20075/0213, UK/H/3524/004/DC). This is a prescription-only medicine (POM).

Atrolak XL contains a substance called quetiapine. This belongs to a group of medicines called anti-psychotics. Atrolak XL can be used to treat several illnesses, such as:

• Schizophrenia: where you 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 you may feel very excited, elated, agitated, enthusiastic or hyperactive or have poor judgement including being aggressive or disruptive.
• Bipolar depression and major depressive episodes in major depressive disorder: where you feel sad. You may find that you feel depressed, feel guilty, lack energy, lose your 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.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Atrolak XL 50 mg prolonged-release Tablets outweigh the risks. Hence a Marketing Authorisation has been granted.

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Module 1
Information about initial procedure

Product Name	Atrolak XL 50 mg prolonged-release tablets
Type of Application	Generic, Article 10(1)
Active Substance	Quetiapine fumarate
Form	Prolonged-release tablets
Strength	50 mg
MA Holder	Accord Healthcare Limited Sage House, 319, Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom
RMS	UK
CMS	Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Latvia, Malta, Norway, Poland, Portugal, Republic of Ireland, Romania, Slovak Republic, Slovenia, Spain, Sweden and The Netherlands
Procedure Numbers	UK/H/3524/004/DC
Timetable	Day 210 – 28th May 2013

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

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

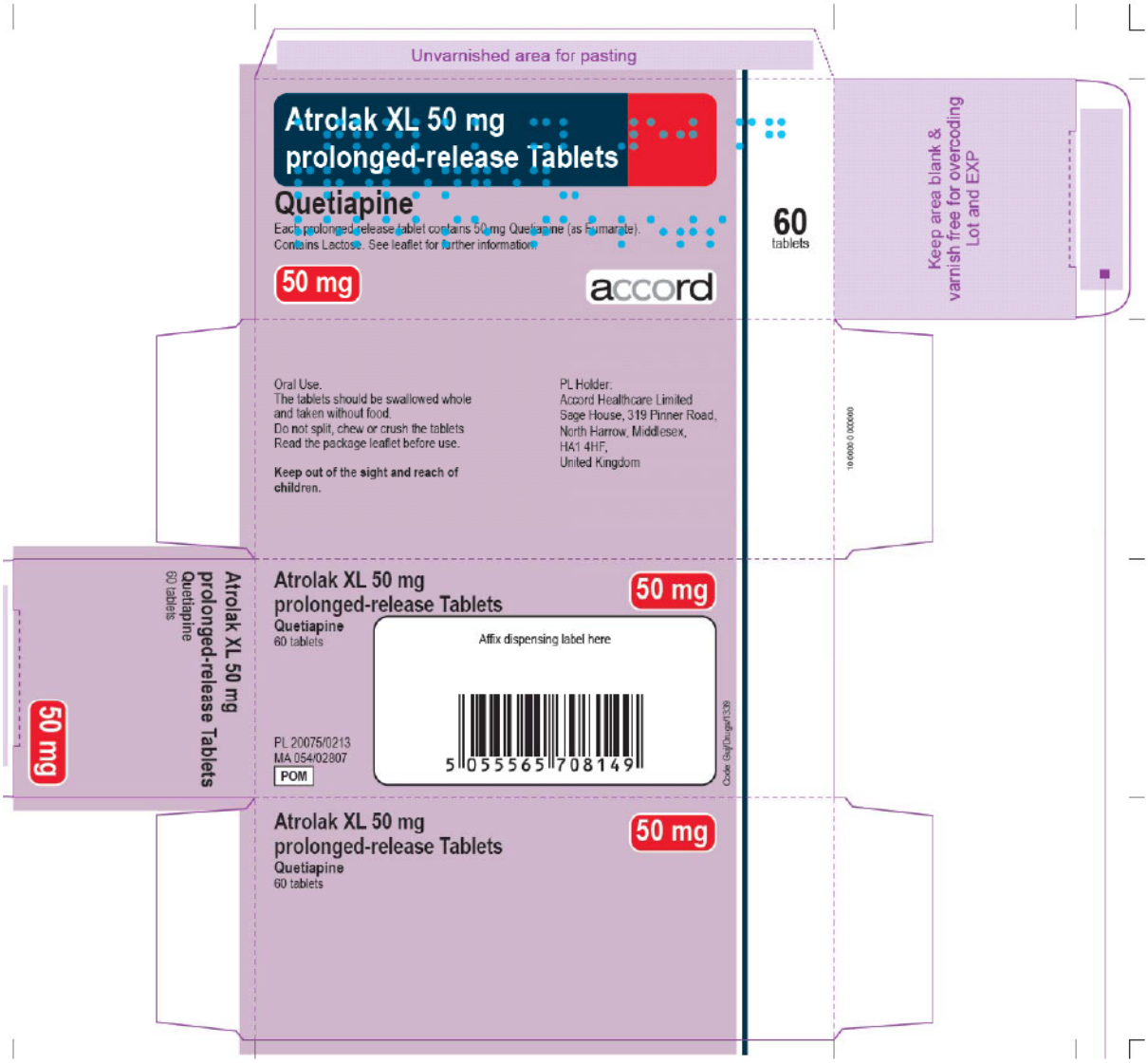
Module 3

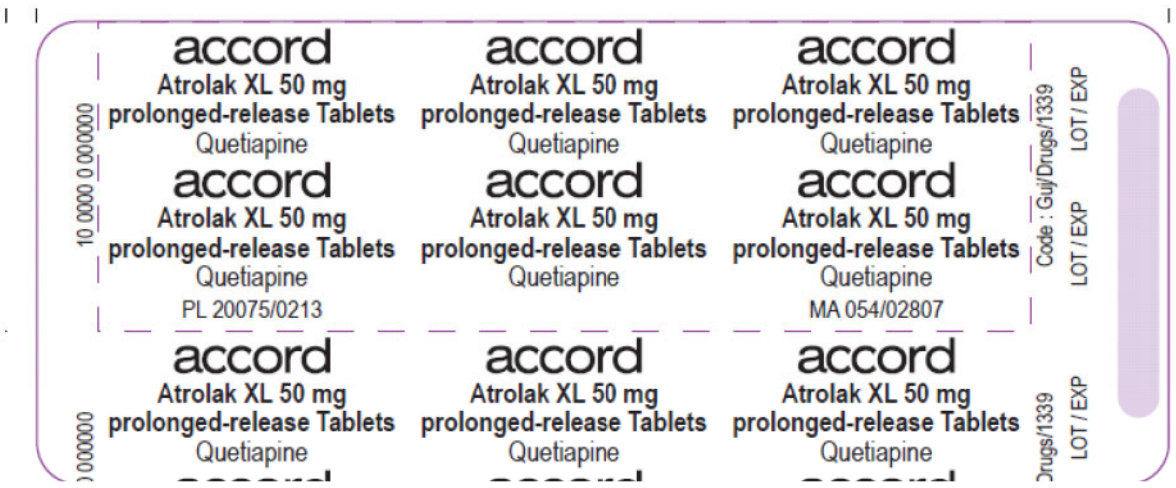
PATIENT INFORMATION LEAFLET

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

Module 4

Labelling




accord
Atrolak XL 50 mg
prolonged-release Tablets
Quetiapine
PL 20075/0213
MA 054/02807
LOT / EXP
Code : Guj/Drugs/1339

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the application for Atrolak XL 50 mg prolonged-release Tablets could be approved for the following indications.

- treatment of Schizophrenia, including:
  - Preventing relapse in stable schizophrenic patients who have been maintained on Atrolak XL 50 mg.
- 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 in patients with bipolar disorder, in patients whose manic or depressive episode has 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. Prior to initiating treatment, clinicians should consider the safety profile of Atrolak XL 50 mg.

This application was submitted under article 10(1) of Directive 2001/83/EC, as amended, for Atrolak XL 50 mg prolonged-release Tablets. The originator product is Seroquel 200 mg tablets (PL 17901/0040) authorised to Astra Zeneca UK Limited, on 31st July 1997.
The reference product for this medicinal product is Seroquel XL 50 mg prolonged release tablets (PL 17901/0249), which was also licensed to Astra Zeneca UK Limited on 10th September 2008.

With UK as the RMS in this Decentralised Procedure (UK/H/3524/004/DC), Accord Healthcare Limited applied for the Marketing Authorisation for Atrolak XL 50 mg prolonged-release Tablets in Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Latvia, Malta, Norway, Poland, Portugal, Republic of Ireland, Romania, Slovak Republic, Slovenia, Spain, Sweden and The Netherlands.

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quctiapinc and norquctiapinc cxhibit affinity for brain scrotonin ($5HT_2$) and dopaminc D1- and D2- receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal undesirable effect (EPS) liability of Quetiapine Prolonged-release Tablets compared to typical antipsychotics. Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2-and serotonin $5HT_1A$ receptors. Quetiapine has no appreciable affinity at muscarinic or benzodiazepine receptors.

No new non-clinical or clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Three bioequivalence studies were submitted to support this application, comparing the applicant's test product Quetiapine 50 mg prolonged-release Tablets (Intas Pharmaceutical Limited, India) with the reference product Seroquel XL 50 mg prolonged-release tablets. These studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product. 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 or 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 considers that 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 the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A Risk Management Plan has been set for the reference product, with some provisions that also need to be applied for generic products. A formal Risk Management Plan is not considered necessary but the applicant has provided a commitment to comply with the special measures for quetiapine.

All member states agreed to grant a licence for the above product at the end of procedure (Day 210 – 28th May 2013). After a subsequent national phase, the UK granted a licence (PL 20075/0213) for this product on 19th June 2013.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Atrolak XL 50 mg prolonged-release Tablets
Name(s) of the active substance(s) (INN)	Quetiapine fumarate
Pharmacotherapeutic classification (ATC code)	Group: Antipsychotics; Diazepines, oxazepines and thiazepines ATC Code: N05A H04.
Pharmaceutical form and strength(s)	Prolonged-release Tablet, 50 mg
Reference numbers for the Decentralised Procedures	UK/H/3524/004/DC
Reference Member State	United Kingdom
Concerned Member States	Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Latvia, Malta, Norway, Poland, Portugal, Republic of Ireland, Romania, Slovak Republic, Slovenia, Spain, Sweden and The Netherlands
Marketing Authorisation Number(s)	PL 20075/0213
Name and address of the authorisation holder	Accord Healthcare Limited Sage House, 319, Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

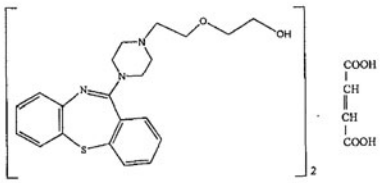
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Quetiapine fumarate

Chemical Names:
11-[4-[2-(2-Hydroxyethoxy) ethyl]-1-piperazinyl] dibenzo [b, f] [1,4] thiazepine fumarate or
2-[2-(4-dibenzo[b,f]-[1,4thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol fumarate

Structure:



Molecular Formula: $(C_{21}H_{25}N_3O_2S)_2 \cdot C_4H_4O_4$
Molecular Weight: 883.1 g/mol

Appearance: A white to off white powder.
Solubility: The substance is soluble in dimethylformamide and in glacial acetic acid, and sparingly soluble in methanol.

Quetiapine fumarate is not the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory 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 drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

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

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, hypromellose, sodium chloride, povidone K-30, silicified microcrystalline cellulose (siliciumdioxide & microcrystalline cellulose), talc, magnesium stearate making up the tablet core; and film-coat consisting of Opadry II 85F540003 Pink (poly (vinyl alcohol), titanium dioxide (E171), macrogol 3350 (E1521), talc, iron oxide red (E172), iron oxide yellow (E172)).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Opadry II 85F540003 Pink which complies with an in-house specification and silicified microcrystalline cellulose which is covered by a United States Pharmacopoeia-National Formulary. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

Pharmaceutical Development

The objective of the development programme was to formulate robust and stable prolonged-release tablets that contain the same active ingredient as Seroquel XL 50 mg prolonged-release tablets (Astra Zeneca UK Limited).

Comparative impurity and dissolution profiles have been presented for the test and reference products.

Manufacture

A 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 and has shown satisfactory results. Process validation data on full-scale commercial batches have been provided. The results are satisfactory.

Finished Product Specification

The finished product specification is satisfactory. Test methods have been described and adequately validated. 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

The finished product is packed in polyvinylchloride (PVC)/polyvinyldichloride (PVDC)-Aluminium (Alu) blister pack or orientated polyamide (OPA)/Alu/PVC – Aluminium blister pack containing 6, 10, 20, 28, 30, 50, 60, 90 and 100 tablets per pack. Not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 30 months with no special storage conditions has been set. This is satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and label are pharmaceutically acceptable.

The applicant did not provide a user testing report in support of this application. However as the applicant has amended the PIL to bring it in-line with the PIL approved for the other approved strengths, an approach bridging the user testing results for the approved strengths to Atrolak XL 50 mg prolonged-release Tablets can be accepted.

The Marketing Authorisation Holder has committed to submit mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Marketing Authorisation Application (MAA) Form
The MAA form is pharmaceutically satisfactory.

Expert report/Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of quetiapine fumarate are well known.

No new non-clinical data have been supplied with this application and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of an environmental risk assessment. This was satisfactory.

There are no objections to the approval of this product from a non-clinical point of view.

III.3 CLINICAL ASPECTS

Clinical Pharmacology
Pharmacokinetics
In support of this application, three bioequivalence studies have been submitted:

Study 1: Single dose 50mg Tablet Bioequivalence Study under Fasting Conditions (437-10)

This is an open label, balanced, randomised, two-treatment, two period, two-sequence, single dose, cross over, comparative oral bioavailability study of Quetiapine 50 mg

prolonged-release Tablets (Intas Pharmaceutical Limited, India) versus the reference product Seroquel XL 50 mg prolonged-release tablets (AstraZeneca UK Ltd, UK) in healthy adult male subjects under fasting conditions.

Blood samples were taken for plasma levels pre-dose and at 1.0, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 14.0, 16.0, 20.0, 24.0 and 36.0 hours after drug administration. There was a washout period of 7 days between study drug administrations.

Geometric Least Square Mean, Ratios and 90% Confidence Interval for quetiapine (n=54)

Parameter (Units)	(Ln-transformed) Geometric Least Square Mean			90% Confidence Interval (Parametric)
	Test product -A	Reference product-B	Ratio (A/B)%	
C_{max} (ng/mL)	65.033	69.920	93.0	85.43 – 101.26%
AUC_{0-t} (ng.h/ml)	924.26	1001.062	92.3	85.92 – 99.21%
AUC_{0-inf} (ng.h/ml)	1006.087	1065.058	94.5	88.00 – 101.40%

The 90% confidence intervals for C_{max} and AUC were within the pre-defined limits acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Quetiapine 50 mg prolonged-release Tablets) and the reference formulation (Seroquel XL 50 mg prolonged-release tablets) under fasting conditions.

Study 2: Single dose 50mg Tablet Bioequivalence Study under Fed Conditions (438-10)

This is an open label, balanced, randomised, two-treatment, two period, two-sequence, single dose, cross over, comparative oral bioavailability study of Quetiapine 50 mg prolonged-release Tablets (Intas Pharmaceutical Limited, India) versus the reference product Seroquel XL 50 mg prolonged-release tablets (AstraZeneca UK Ltd, UK) in healthy adult male subjects under fed conditions.

Blood samples were taken for plasma levels pre-dose and at 1.0, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 14.0, 16.0, 20.0, 24.0 and 36.0 hours after drug administration. There was a washout period of 7 days between study drug administrations.

Geometric Least Squares Mean, Ratios and 90% Confidence Interval for quetiapine (n=75).

Parameter (Units)	(Ln-transformed) Geometric Least Square Mean			90% Confidence Interval (Parametric)
	Test product -A	Reference product-B	Ratio (A/B)%	
C_{max} (ng/mL)	119.698	130.093	92.0	86.37 – 98.02%
AUC_{0-t} (ng.h/ml)	1166.636	1198.968	97.3	93.89 – 100.84%
AUC_{0-inf} (ng.h/ml)	1224.831	1252.622	97.8	94.05 – 101.66%

The 90% confidence intervals for C_{max} and AUC were within the pre-defined limits acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test

formulation (Quetiapine 50 mg prolonged-release Tablets) and the reference formulation (Seroquel XL 50 mg prolonged-release tablets) under fed conditions.

Study 3: Multiple dose steady state 50 mg Tablet Bioequivalence Study under Fasting Conditions (439-10)

This is an open label, balanced, randomised, two-treatment, two period, two-sequence, cross over, comparative oral bioavailability study of Quetiapine 50 mg prolonged-release Tablets (Intas Pharmaceutical Limited, India) versus the reference product Seroquel XL 50 mg prolonged-release tablets (AstraZeneca UK Ltd, UK) after multiple dose administration at steady state in healthy adult male subjects under fasting conditions.

Blood samples were taken for plasma levels pre-dose and at 1.0, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 14.0, 16.0, 20.0 and 24.0 hours after drug administration. There was a washout period of 7 days between study drug administrations.

Geometric Least Squares Mean, Ratios and 90% Confidence Interval for quetiapine (n=56)

Parameter (Units)	(Ln-transformed) Geometric Least Square Mean			90% Confidence Interval (Parametric)
	Test product -A	Reference product-B	Ratio (A/B)%	
$C_{min,ss}$ (ng/mL)	12.336	13.436	91.8	80.55 – 104.65%
$AUC_{max,ss}$(ng/ml)	69.024	77.553	89.0	82.60 – 95.91%
$AUC_{T,ss}$(ng.h/ml)	926.983	979.638	94.6	88.62 – 101.04%

The 90% confidence intervals for C_{max} and AUC were within the pre-defined limits acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Quetiapine 50 mg prolonged-release Tablets) and the reference formulation (Seroquel XL 50 mg prolonged-release tablets) after multiple dose administration at steady state under fasting conditions.

Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

Clinical Efficacy
No new data have been submitted and none are required.

Clinical Safety
No new data have been submitted and none are required.

Expert Report
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

Marketing Authorisation Application (MAA) Form
The MAA form is medically satisfactory.

Conclusion
There are no objections to the approval of this product from a clinical point of view.

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Atrolak XL 50 mg prolonged-release tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

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

CLINICAL

Bioequivalence has been demonstrated between the applicant's Quetiapine 50 mg prolonged-release Tablets and the reference product, Seroquel XL 50 mg prolonged-release tablets after single dose under fasting and fed conditions and after multiple dose administration at steady state under fasting conditions.

No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE

The SmPC and PIL are satisfactory and consistent with those of the reference product, where appropriate. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with quetiapine fumarate is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is therefore considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome