Public Assessment Report

Decentralised Procedure

Denzapine 50mg / ml Oral Suspension

(clozapine)

UK/H/1926/012/DC

UK licence numbers: PL 06831/0270

Genus Pharmaceuticals Limited

LAY SUMMARY

On 18th February 2009, the MHRA granted Merz Pharma UK Limited a Marketing Authorisation (licence) for the medicinal product Denzapine 50mg / ml Oral Suspension (PL 20286/0013, UK/H/1926/01/DC). The licence underwent a change of ownership to Genus Pharmaceuticals Limited (PL 06831/0270) on 30th January 2012. This is a prescription-only medicine (POM).

Denzapine Oral Suspension contains the active ingredient, clozapine, which belongs to a group of medicines called atypical antipsychotics. It is an antipsychotic agent that is different from classic antipsychotics. Antipsychotics are mainly used to treat schizophrenia. Schizophrenia is a psychiatric disorder that affects the way a person thinks and behaves.

Denzapine Oral Suspension is used to treat: patients with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least 2 different antipsychotic drugs, at least one of which should be a second generation antipsychotic; and psychotic disorders occurring in patients with Parkinson's disease, when standard treatment has failed.

This application is based on a reference product with a valid UK licence. No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Denzapine 50mg / ml Oral Suspension outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about Initial Procedure

Product Name	Denzapine 50mg / ml Oral Suspension
Type of Application	Generic, Article 10.3
Active Substance	Clozapine
Form	Oral Suspension
Strength	50 mg / ml
MA Holder	Merz Pharma UK Ltd 260 Centennial Park Elstree, Herts WD6 3SR UK
Reference Member State (RMS)	UK
Concerned Member State (CMS)	IE
Procedure Number	UK/H/1926/01/DC
Timetable	Day 150 – 16th January 2009

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

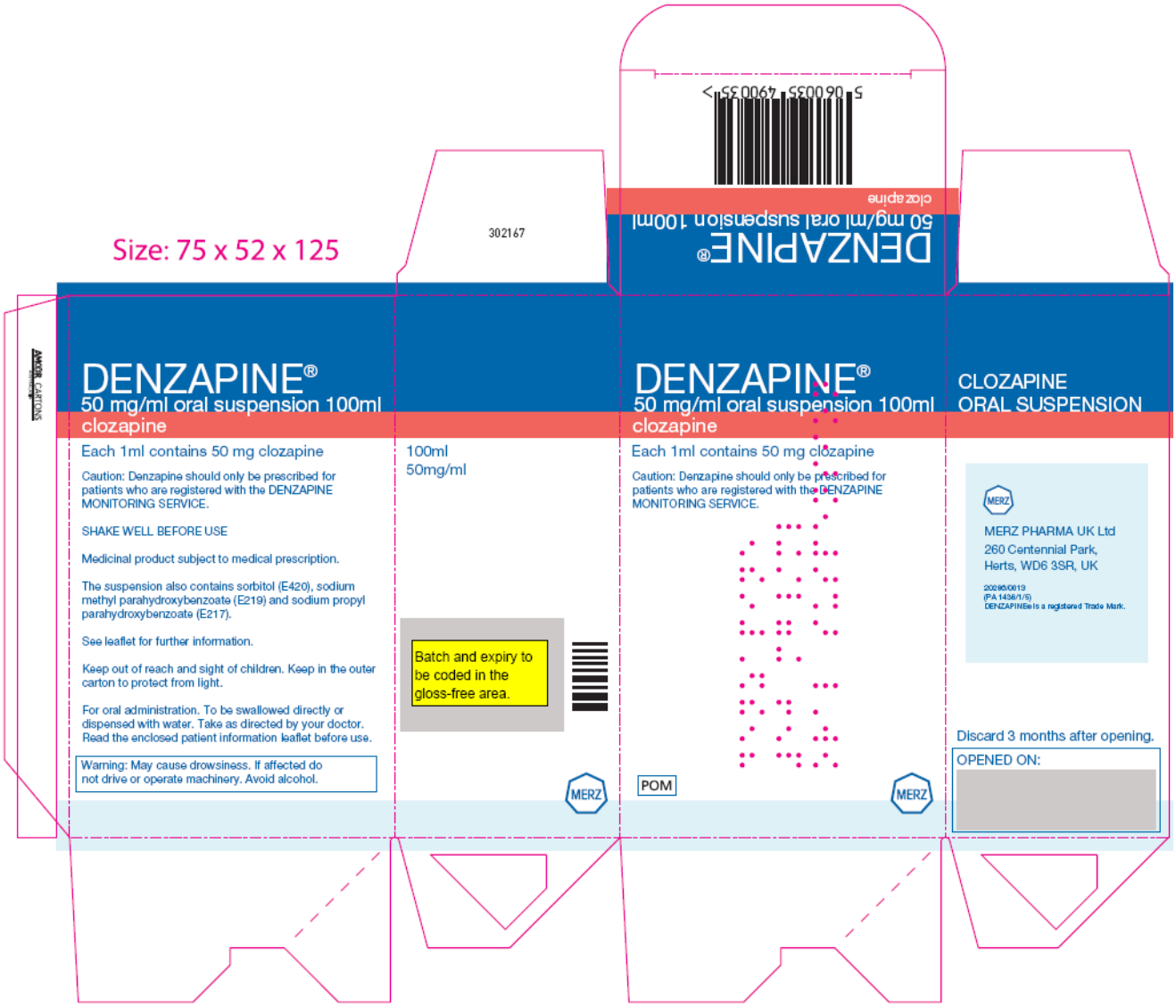
Product Information Leaflet

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

Bottle carton



Bottle label

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Merz Pharma UK Limited a Marketing Authorisation for the medicinal product Denzapine 50mg / ml Oral Suspension (PL 20286/0013, UK/H/1926/01/DC) on 18th February 2009. The product is a prescription-only medicine.

This is an abridged application for Denzapine 50mg / ml Oral Suspension, submitted under Article 10.3 of 2001/83 EC, as amended. The application refers to the reference product, Clozaril Tablets 25mg (PL 00101/0228), authorised to Novartis Pharmaceuticals UK Limited on 22nd December 1989. This is the innovator product. The innovator product has been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

Denzapine Oral Suspension contains the active ingredient, clozapine. Clozapine is a dibenzodiazepine derivative classified as an atypical antipsychotic drug because of its profile of binding to serotonergic as well as dopamine receptors; its effects on various dopamine mediated behaviors also differ from those exhibited by more typical antipsychotics. In particular, clozapine interferes to a lower extent with the binding of dopamine at D1, D2, D3 and D5 receptors, and has a high affinity for the D4 receptor, but it does not induce catalepsy nor inhibit apomorphine-induced stereotypy in animal models as is seen with 'conventional' neuroleptics. This evidence suggests clozapine is preferentially more active at limbic than at striatal dopamine receptors and may explain the relative freedom of clozapine from extrapyramidal side effects together with strong anticholinergic activity.

Although clozapine is well absorbed from the gastrointestinal tract, its bioavailability is limited to about 50% by first-pass metabolism. Peak plasma concentrations are achieved, on average, about 2.5 hours after oral doses. Clozapine is about 95% bound to plasma proteins and has a mean terminal elimination half-life of about 12 hours at steady state. It is almost completely metabolised and routes of metabolism include N-demethylation, hydroxylation, and N-oxidation; the desmethyl metabolite (norclozapine) has limited activity. The metabolism of clozapine is mediated mainly by the cytochrome P450 isoenzyme CYP1A2. Metabolites and trace amounts of unchanged drug are excreted mainly in the urine and also in the faeces. There is wide interindividual variation in plasma concentrations of clozapine and no simple correlation has been found between plasma concentrations and therapeutic effect. It is distributed into breast milk.

Denzapine is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics. Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration. Denzapine is also indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

No new preclinical or clinical efficacy studies were conducted, which is acceptable given that the application cross-refers to a product that has been licensed for over 10 years.

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Denzapine 50mg / ml Oral Suspension (0.25ml of suspension, equivalent to 12.5mg clozapine), to that of the reference product, Clozaril Tablets 12.5mg (half a Clozaril Tablet 25mg - PL 00101/0228, Novartis Pharmaceuticals UK Limited). The bioequivalence study was 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. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. 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.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Denzapine 50mg / ml Oral Suspension
Name(s) of the active substance(s) (INN)	Clozapine
Pharmacotherapeutic classification (ATC code)	Antipsychotic agent (N05A H02)
Pharmaceutical form and strength(s)	Oral Suspension – 50mg / ml
Reference numbers for the Mutual Recognition Procedure	UK/H/1926/01/DC
Reference Member State	United Kingdom
Member States concerned	Ireland
Marketing Authorisation Number(s)	PL 20286/0013
Name and address of the authorisation holder	Merz Pharma UK Ltd 260 Centennial Park Elstree, Herts WD6 3SR UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

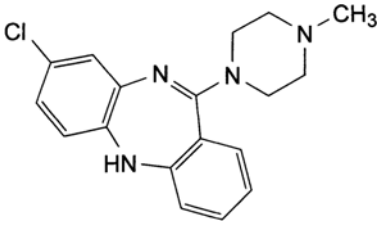
Clozapine

Nomenclature:

INN: Clozapine

Chemical name: 8-chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine

Structure:



Molecular formula: $C_{18}H_{19}ClN_4$

Molecular weight: 326.8

CAS No: 5786-21-0

Physical form: Yellow crystalline powder

Solubility: Practically insoluble in water, freely soluble in methylene chloride, soluble in alcohol

The active substance, clozapine, is the subject of a European Pharmacopeia (EP) monograph.

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 specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate active substance specification has been provided and is in compliance with the EP monograph for clozapine. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. It is packed in double polyethylene bags which are closed and sealed separately and placed into sealed drums. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support a retest period of 2 years.

DRUG PRODUCT

Description and Composition

The drug product is presented as a free flowing yellow suspension. Each 1ml of oral suspension contains 50mg of the active ingredient clozapine.

Other ingredients consist of pharmaceutical excipients, namely glycerol (e422), sodium dihydrogen phosphate dihydrate (e339(i)), sorbitol (e420), xanthan gum (e415), povidone (e1201), sodium methyl parahydroxybenzoate (e219), sodium propyl parahydroxybenzoate (e217), hydrochloric acid (for ph adjustment) (e507), sodium hydroxide (for ph adjustment) (e524), and purified water. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of hydrochloric acid and sodium hydroxide, which comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The glycerol has been confirmed as being of vegetable origin. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Comparative dissolution data were provided for the generic clozapine 50mg / ml suspension and the reference product. The dissolution profiles were found to be similar.

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specification is provided for both release and shelf life and is satisfactory; it provides an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished product is licensed for marketing in amber glass bottles containing 100ml of suspension. The bottle is fitted with a white, polypropylene, round child-resistant, tamper-evident screw cap containing a LDPE foam liner. The bottle is packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. The primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set for the unopened bottles; this is satisfactory. Once opened, the shelf life is 90 days. The product does not require and special storage conditions.

Bioequivalence Study

A bioequivalence study was presented comparing the test product, Denzapine 50mg / ml Oral Suspension (0.25ml of suspension, equivalent to 12.5mg clozapine), to the reference product, Clozaril Tablets 12.5mg (half a Clozaril Tablet 25mg - PL 00101/0228, Novartis Pharmaceuticals UK Limited).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

Expert Report

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

Product Information

The approved SmPC, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling fulfils the statutory requirements for Braille.

Conclusion

The test product is pharmaceutically equivalent to the reference product, which has been licensed in the UK for over 10 years. On this basis, and considering the bioequivalence data provided, the applicant’s claim that Denzapine 50mg / ml Oral Suspension is a hybrid medicinal product of Clozaril Tablets 12.5mg (half a Clozaril Tablet 25mg, Novartis Pharmaceuticals UK Limited) is justified.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation was, therefore, granted.

III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for this application for a hybrid version of a product that has been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacological and toxicological properties of clozapine, which is a widely used and well-known active substance.

III.3 CLINICAL ASPECTS

INDICATIONS

Denzapine is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics. Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration. Denzapine is also indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

The indications are consistent with those for the innovator product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPC.

The posology is consistent with that for the innovator product and is satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for these types of application.

CLINICAL PHARMACOLOGY

The clinical pharmacology of clozapine is well known. No novel pharmacodynamic data are supplied or required for this application.

Pharmacokinetics – bioequivalence study

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profiles of Denzapine 50mg / ml Oral Suspension (test) - 0.25ml of suspension, equivalent to 12.5mg clozapine; and Clozaril Tablets 12.5mg - half a Clozaril Tablet 25mg (broken by hand), PL 00101/0228, Novartis Pharmaceuticals UK Limited (reference). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for both the test and reference product. No liquid formulation of clozapine is currently commercially available. The low strength of Clozapine 12.5mg was selected because of safety / tolerability reasons associated with healthy subjects being treated with higher strengths. This was considered satisfactory.

This was a randomised, open-label, two-treatment, two-period, two-sequence, single dose crossover bioavailability and bioequivalence study conducted in 24 healthy adult human male and female subjects under fasting conditions. A single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 7 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 72.0 hours after administration of test or reference product. Plasma levels of clozapine and its metabolite norclozapine were detected by a validated LC/MS method.

The primary pharmacokinetic parameters for this study were C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Results:

24 subjects were included in the study and all were included in PK and statistical analysis. There were no drop-outs. No serious or significant adverse events were reported during the study.

The summary of the results of the bioequivalence study are tabulated below:

Pharmacokinetic results for a randomised, two-way, single dose crossover study between the test and reference products. n=24 healthy subjects, dosed fasted; t=72 hours. Wash-out period: 7 days. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD) – Clozapine

Tab. 2.5.2.A: Summary of pharmacokinetic data for clozapine (single dose of 12.5 mg; n = 24)

Pharmacokinetic Parameters	**Clozapine 50 mg/ml suspension** (Test): 0.25 ml suspension equivalent to 12.5 mg (mean ± SD)	Clozaril® 25 mg Tablet (Reference): one half tablet equivalent to 12.5 mg (mean ± SD)
AUC_{0-inf} [ng/ml·h]	437.11 ± 145.63	456.28 ± 184.01
AUC_{0-t} [ng/ml·h]	417.26 ± 133.96	433.94 ± 171.10
C_{max} [ng/ml]	34.93 ± 8.78	35.59 ± 9.37
t_{max} [h]	1.38 ± 0.59	1.67 ± 0.84
$t_{½}$ [h]	17.38 ± 2.63	17.99 ± 2.59

Tab. 2.5.2.B: Statistical analysis - Test versus Reference

Geometric mean ratio (%)		90% Confidence interval	
AUC_{0-inf}	98.37	$Log_{10}(AUC_{0-inf})$	0.918 to 1.054*
AUC_{0-t}	98.80	$Log_{10}(AUC_{0-t})$	0.922 to 1.059
C_{max}	98.49	$Log_{10}(C_{max})$	0.923 to 1.051*
* The 90% CIs for the log-transformed AUC_{0-inf} and C_{max} are within the bioequivalence criteria of 0.80 to 1.25			

Conclusion on Bioequivalence

The results of the bioequivalence study show that the test product and reference product are bioequivalent, under fasting conditions, as the confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ fall within the acceptance criteria ranges of 80-125% in line with current CHMP guidelines. It is concluded that bioequivalence between the test suspension formulation and the reference Clozaril tablets formulation has been shown.

Clinical efficacy

No new data have been submitted and none are required. Efficacy is reviewed in the clinical overview. The efficacy of clozapine is well-established from its extensive use in clinical practice.

Clinical safety

No new data have been submitted and none are required for applications of this type. Safety is reviewed in the clinical overview. The safety profile of clozapine is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The final SmPC is consistent with that for the innovator product, and is acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPC and is satisfactory.

Labelling

The labelling is satisfactory.

Expert report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (0.25ml of Denzapine 50mg / ml Oral Suspension, equivalent to 12.5mg clozapine) and reference (Clozaril Tablets 12.5mg: half a Clozaril Tablet 25mg - PL 00101/0228, Novartis Pharmaceuticals UK Limited) products within general acceptance limits.

Sufficient clinical information has been submitted to support this application. A Marketing Authorisation was, therefore, granted on medical grounds.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

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

PRECLINICAL

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

EFFICACY

Bioequivalence has been demonstrated between the applicant's Denzapine 50mg / ml Oral Suspension (0.25ml of suspension, equivalent to 12.5mg clozapine), and the reference product, Clozaril Tablets 12.5mg (half a Clozaril Tablet 25mg - PL 00101/0228, Novartis Pharmaceuticals UK Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and consistent with those for the innovator product.

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

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study and other data provided support the claim that the applicant's Denzapine 50mg / ml Oral Suspension is a hybrid version of the reference product, Clozaril Tablets 25mg (Novartis Pharmaceuticals UK Limited). Extensive clinical experience with clozapine is considered to have demonstrated the therapeutic value of the active substance. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

The following table lists some non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	Application type	Scope	Outcome
17/06/2013	VAR Medical Type IB	To update section 4.2 (posology and method of administration) of the SmPC in line with revised instructions for use for the suspension. As a consequence, the PIL has been updated.	09/08/2013

Annex 1

Reference: **PL 06831/0270- 0015**

Product: **Denzapine 50 mg /ml Oral Suspension**

MAH: **Genus Pharmaceuticals**

Active Ingredient: **Clozapine**

Reason:
To update section 4.2 (posology and method of administration) of the SmPC in line with revised instructions for use for the suspension. As a consequence, the PIL has been updated

Supporting evidence:
The applicant has submitted the following documents:

Quality information
Existing and proposed SmPC
Existing and proposed PIL

Evaluation
Adequate information has been provided.

Conclusion
The variation was approved on 9th August 2013 and the updated SmPC fragment and the PIL have been incorporated into this Marketing Authorisation. The proposed changes are acceptable.

The current approved UK version of the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for this product are available on the MHRA website.