Public Assessment Report

Decentralised Procedure

Denzapine 50mg tablets
Denzapine 200mg tablets

(clozapine)

UK/H/1463/01-02/DC
UK licence numbers: PL 20286/0011 & 0012

Merz Pharma UK Ltd
LAY SUMMARY

On 16th February 2009, the MHRA granted Merz Pharma UK Limited Marketing Authorisations (licences) for the medicinal products Denzapine 50mg and 200mg tablets (PL 20286/0011-0012, UK/H/1463/01-02/DC). These are prescription-only medicines (POM).

Denzapine Tablets contain 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 Tablets are 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.

These applications are based on reference products with valid UK licences. No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Denzapine 50mg and 200mg tablets outweigh the risks; hence Marketing Authorisations have been granted.
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Module 1

Information about Initial Procedure

| Product Name       | Denzapine 50mg tablets  
|                   | Denzapine 200mg tablets |
| Type of Application | Generic, Article 10.3  |
| Active Substance   | Clozapine              |
| Form               | tablets                |
| Strength           | 50mg and 200mg         |
| MA Holder          | Merz Pharma UK Ltd     
|                   | 260 Centennial Park    
|                   | Elstree, Herts         
|                   | WD6 3SR                
|                   | UK                     |
| Reference Member State (RMS) | UK |
| Concerned Member State / s (CMS) | IE |
| Procedure Number   | UK/H/1463/01-02/DC     |
| Timetable          | Day 150 – 16th January 2009 |
Module 2
Summary of Product Characteristics

Denzapine 50mg & 200mg tablets (PL 20286/0011-0012)
Differences are indicated in blue text

1 NAME OF THE MEDICINAL PRODUCT

Denzapine 50 mg Tablets / Denzapine 200 mg Tablets

DENZAPINE can cause agranulocytosis. Its use should be limited to patients:

• with schizophrenia who are non-responsive to or intolerant of antipsychotic drug treatment, or with psychosis in Parkinson’s disease when other treatment strategies have failed (see point 4.1)

• who have initially normal leukocyte findings (white blood cell count of >3500/mm$^3$ (3.5 x $10^9$/L), and an absolute neutrophil count (ANC) of >2000/mm$^3$ (2.0 x $10^9$/L)), and

• in whom regular white blood cell (WBC) counts and absolute neutrophil counts (ANC) can be performed as follows: weekly during the first 18 weeks of therapy, and at least every 4 weeks thereafter throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of DENZAPINE.

Prescribing physicians should comply fully with the required safety measures. At each consultation, a patient receiving DENZAPINE should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia.

DENZAPINE must be dispensed under strict medical supervision in accordance with official recommendations.

Myocarditis

Clozapine is associated with an increased risk of myocarditis which has, in rare cases, been fatal. The increased risk of myocarditis is greatest in the first 2 months of treatment. Fatal cases of cardiomyopathy have also been reported rarely.

Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first 2 months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea) or symptoms that mimic myocardial infarction.

If myocarditis or cardiomyopathy are suspected, DENZAPINE treatment should be promptly stopped and the patient immediately referred to a cardiologist.

Patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50mg / 200mg Clozapine.

Each Denzapine 50 mg / 200mg Tablet also contains 65mg / 260mg of lactose monohydrate.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

Round, flat yellow, bevel edged tablets embossed with “50” over a pressure sensitive breakline on one face, the other face plain.

Large, oval-shaped yellow tablets with “200” on one side and a breakline on the other side.

The breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DENZAPINE is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreated 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.

4.2 Posology and method of administration

Method of Administration – Oral

The dosage must be adjusted individually. For each patient the lowest effective dose should be used. Initiation of DENZAPINE treatment must be restricted to those patients with a WBC count over 3500/mm³ (3.5 x 10⁹/L) and an absolute neutrophil count (ANC) greater than 2000/mm³ (2.0 x 10⁹/L) within standardised normal limits.

Dose adjustment is indicated in patients who are also receiving medicinal products that have pharmacodynamic and pharmacokinetic interactions with DENZAPINE, such as benzodiazepines or selective serotonin re-uptake inhibitors (see section 4.5 Interaction with other medicinal products and other forms of interaction).

The following dosages are recommended:

Treatment-resistant schizophrenic patients

Starting therapy
12.5 mg (half a 25 mg tablet) once or twice on the first day, followed by one or two 25 mg tablets on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 to 100 mg at half-weekly or, preferably, weekly intervals.

Use in children
Not Recommended in Children.

Use in the elderly
Initiation of treatment is recommended at a particularly low dose (12.5 mg given once on the first day), with subsequent dose increments restricted to 25 mg/day.

Therapeutic dose range
In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. The total daily dose may be divided unevenly, with the larger portion at bedtime. For maintenance dose, see below.

Maximum dose
To obtain full therapeutic benefit, a few patients may require larger doses, in which case judicious increments (i.e. not exceeding 100 mg) are permissible up to 900 mg/day. The possibility of increased adverse reactions (in particular seizures) occurring at doses over 450 mg/day must be borne in mind.

Maintenance dose
After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration is therefore recommended. Treatment should be maintained for at least 6 months. If the daily dose does not exceed 200 mg, once daily administration in the evening may be appropriate.
**Ending therapy**

In the event of planned termination of DENZAPINE therapy, a gradual reduction in dose over a 1- to 2-week period is recommended. If abrupt discontinuation is necessary (e.g. because of leucopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound, such as profuse sweating, headache, nausea, vomiting and diarrhoea.

**Re-starting therapy**

In patients in whom the interval since the last dose of DENZAPINE exceeds 2 days, treatment should be re-initiated with 12.5 mg (half a 25 mg tablet) given once or twice on the first day. If this dose is well tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment. However, in any patient who has previously experienced respiratory or cardiac arrest with initial dosing (see section 4.4 Special warnings and precautions for use), but was then able to be successfully titrated to a therapeutic dose, re-titration should be carried out with extreme caution.

**Switching from a previous antipsychotic therapy to DENZAPINE**

It is generally recommended that DENZAPINE should not be used in combination with other antipsychotics, including depot preparations, which may have a myelosuppressive effect. When DENZAPINE therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the other antipsychotic should first be discontinued by tapering the dosage downwards.

**Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed**

The starting dose must not exceed 12.5 mg/day (half a 25 mg tablet), taken in the evening. Subsequent dose increases must be by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, a dose that cannot be reached until the end of the second week. The total daily amount should preferably be given as a single dose in the evening.

The mean effective dose is usually between 25 and 37.5 mg/day. In the event that treatment for at least one week with a dose of 50 mg fails to provide a satisfactory therapeutic response, dosage may be cautiously increased by increments of 12.5 mg/week.

The dose of 50 mg/day should only be exceeded in exceptional cases, and the maximum dose of 100 mg/day must never be exceeded.

Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment.

When there has been complete remission of psychotic symptoms for at least 2 weeks, an increase in anti-parkinsonian medication is possible if indicated on the basis of motor status. If this approach results in the recurrence of psychotic symptoms, DENZAPINE dosage may be increased by increments of 12.5 mg/week up to a maximum of 100 mg/day, taken in one or two divided doses (see above).

Ending therapy: A gradual reduction in dose by steps of 12.5 mg over a period of at least one week (preferably two) is recommended.

Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis as indicated in section 4.4 (Special warnings and precautions for use). In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

### 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactose intolerance deficiency or glucose-galactose malabsorption should not take this medicine.
- Patients unable to undergo regular blood tests.
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
- History of DENZAPINE-induced agranulocytosis.
• Impaired bone marrow function.
• Uncontrolled epilepsy.
• Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
• Circulatory collapse and/or CNS depression of any cause.
• Severe renal or cardiac disorders (e.g. myocarditis).
• Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
• Paralytic ileus.
• DENZAPINE treatment must not be started concurrently with drugs known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be discouraged.

4.4 Special warnings and precautions for use

Precautions
DENZAPINE can cause agranulocytosis. The incidence of agranulocytosis and the fatality rate in those developing agranulocytosis have decreased markedly since the institution of WBC counts and ANC monitoring. The following precautionary measures are therefore mandatory and should be carried out in accordance with official recommendations.

Because of the risks associated with DENZAPINE, its use is limited to patients in whom therapy is indicated as set out in section 4.1 (Therapeutic indications) and:

- who have initially normal leukocyte findings (WBC count greater than 3500/mm³ (3.5 x 10⁹/L) and ANC above 2000/mm³ (2.0 x 10⁹/L), and
- in whom regular WBC counts and ANC can be performed weekly for the first 18 weeks and at least 4-week intervals thereafter. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of DENZAPINE.

Before initiating clozapine therapy patients should have a blood test (see “agranulocytosis”) and a history and physical examination. Patients with history of cardiac illness or abnormal cardiac findings on physical examination should be referred to a specialist for other examinations that might include an ECG, and the patient treated only if the expected benefits clearly outweigh the risks (see Section 4.3). The treating physician should consider performing a pre-treatment ECG. Caution should be exercised in patients with cardiovascular disease or a family history of QT prolongation.

The concomitant administration of neuroleptic medicines should be avoided.

An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. DENZAPINE should be used with caution in patients with risk factors for stroke.

Prescribing physicians should comply fully with the required safety measures.
to keep a record of all patients' blood results and to take any steps necessary to prevent these patients from accidentally being rechallenged in the future.

Patients with a history of primary bone marrow disorders may be treated only if the benefit outweighs the risk. They should be carefully reviewed by a haematologist prior to starting DENZAPINE.

Patients who have low WBC counts because of benign ethnic neutropenia should be given special consideration and may be started on DENZAPINE with the agreement of a haematologist.

**WBC Counts and ANC Monitoring**

WBC and differential blood counts must be performed within 10 days prior to initiating DENZAPINE treatment to ensure that only patients with normal WBC counts (WBC count greater than 3500/mm³ (3.5 x 10⁹/L) and ANC above 2000/mm³ (2.0 x 10⁹/L)) will receive the drug. After the start of DENZAPINE treatment the WBC count and ANC must be monitored weekly for the first 18 weeks, and at least at four-week intervals thereafter.

Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of DENZAPINE or until haematological recovery has occurred (see below Low WBC count/ANC). At each consultation, the patient should be reminded to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. WBC and differential blood counts must be performed immediately if any symptoms or signs of an infection occur.

**Low WBC count/ANC**

If, during DENZAPINE therapy, either the WBC count falls to between 3500/mm³ (3.5 x 10⁹/L) and 3000/mm³ (3.0 x 10⁹/L) or the ANC falls to between 2000/mm³ (2.0 x 10⁹/L) and 1500/mm³ (1.5 x 10⁹/L), haematological evaluations must be performed at least twice weekly until the patient's WBC count and ANC stabilise within the range 3000-3500/mm³ (3.0 - 3.5 x 10⁹/L) and 1500 - 2000/mm³ (1.5 - 2.0 x 10⁹/L), respectively, or higher.

Immediate discontinuation of DENZAPINE treatment is mandatory if either the WBC count is less than 3000/mm³ (3.0 x 10⁹/L) or the ANC is less than 1500/mm³ (1.5 x 10⁹/L) during DENZAPINE treatment. WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Confirmation of the haematological values is recommended by performing two blood counts on two consecutive days; however, DENZAPINE should be discontinued after the first blood count.

Following discontinuation of DENZAPINE, haematological evaluation is required until haematological recovery has occurred.

<table>
<thead>
<tr>
<th>Blood cell count</th>
<th>Action required</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC/mm³ (/L)</td>
<td>ANC/mm³ (/L)</td>
</tr>
<tr>
<td>&gt;3500 (3.5 x 10⁹)</td>
<td>&gt;2000 (2.0 x 10⁹)</td>
</tr>
<tr>
<td>3000-3500 (3.0 x 10⁹ - 3.5 x 10⁹)</td>
<td>1500-2000 (1.5 x 10⁹ - 2.0 x 10⁹)</td>
</tr>
<tr>
<td>&lt; 3000 (&lt;3.0 x 10⁹)</td>
<td>&lt; 1500 (&lt;1.5 x 10⁹)</td>
</tr>
</tbody>
</table>

If DENZAPINE has been withdrawn and either a further drop in the WBC count below 2000/mm³ (2.0 x 10⁹/L) occurs or the ANC falls below 1000/mm³ (1.0 x 10⁹/L), the management of this condition must be guided by an experienced haematologist.

**Discontinuation of therapy for haematological reasons**

Patients in whom DENZAPINE has been discontinued as a result of either WBC or ANC deficiencies (see above) must not be re-exposed to DENZAPINE.

Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent the patient being accidentally rechallenged in the future.
Discontinuation of therapy for other reasons
Patients who have been on DENZAPINE for more than 18 weeks and have had their treatment interrupted for more than 3 days but less than 4 weeks should have their WBC count and ANC monitored weekly for an additional 6 weeks. If no haematological abnormality occurs, monitoring at intervals not exceeding 4 weeks may be resumed. If DENZAPINE treatment has been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment and the dose should be re-titrated (see section 4.2 Posology and method of administration).

Other precautions
In the event of eosinophilia, discontinuation of DENZAPINE is recommended if the eosinophil count rises above 3000/mm³ (3.0 x 10⁹/L); therapy should be restarted only after the eosinophil count has fallen below 1000/mm³ (1.0 x 10⁹/L).

In the event of thrombocytopenia, discontinuation of DENZAPINE therapy is recommended if the platelet count falls below 50 000/mm³ (50 x 10⁹/L).

Orthostatic hypotension, with or without syncope, can occur during DENZAPINE treatment. Rarely, collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur with concurrent use of benzodiazepine or any other psychotropic agent (see section 4.5 Interaction with other medicinal products and other forms of interaction) and during initial titration in association with rapid dose escalation; on very rare occasions they may occur even after the first dose. Therefore, patients commencing DENZAPINE treatment require close medical supervision. Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease.

Analysis of safety databases suggests that the use of clozapine is associated with an increased risk of myocarditis especially during, but not limited to, the first two months of treatment. Some cases of myocarditis have been fatal.

Pericarditis/pericardial effusion and cardiomyopathy have also been reported in association with clozapine use; these reports also include fatalities. Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first two months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea), or symptoms that mimic myocardial infarction. Other symptoms which may be present in addition to the above include flu-like symptoms. If myocarditis or cardiomyopathy are suspected, DENZAPINE treatment should be promptly stopped and the patient immediately referred to a cardiologist.

Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to DENZAPINE.

Patients with a history of epilepsy should be closely observed during DENZAPINE therapy since dose-related convulsions have been reported. In such cases, the dose should be reduced (see section 4.2 Posology and method of administration) and, if necessary, an anti-convulsant treatment should be initiated.

Patients with stable pre-existing liver disorders may receive DENZAPINE, but need regular liver function tests. Liver function tests should be performed in patients in whom symptoms of possible liver dysfunction, such as nausea, vomiting and/or anorexia, develop during DENZAPINE therapy. If the elevation of the values is clinically relevant (more than 3 times the UNL) or if symptoms of jaundice occur, treatment with DENZAPINE must be discontinued. It may be resumed (see “Re-starting therapy” under section 4.2) only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of the drug.

DENZAPINE exerts anticholinergic activity, which may produce undesirable effects throughout the body. Careful supervision is indicated in the presence of prostatic enlargement and narrow-angle glaucoma. Probably on account of its anticholinergic properties, clozapine has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction and paralytic ileus (see section 4.8 Undesirable effects). On rare occasions these cases have been fatal. Particular care is necessary in patients who are receiving concomitant medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and antiparkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation. It is vital that constipation is recognised and actively treated.
During DENZAPINE therapy, patients may experience transient temperature elevations above 38°C, with the peak incidence within the first 3 weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered.

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. A mechanism for this possible association has not yet been determined. Cases of severe hyperglycaemia with ketoacidosis or hyperosmolar coma have been reported very rarely in patients with no prior history of hyperglycaemia, some of which have been fatal. When follow-up data were available, discontinuation of clozapine resulted mostly in resolution of the impaired glucose tolerance, and reinstitution of clozapine resulted in its reoccurrence. The discontinuation of clozapine should be considered in patients where active medical management of their hyperglycaemia has failed.

Since DENZAPINE may be associated with thromboembolism, immobilisation of patients should be avoided.

Use in the elderly
Initiation of treatment in the elderly is recommended at a lower dose (see section 4.2 Posology and method of administration).

Orthostatic hypotension can occur with DENZAPINE treatment and there have been reports of tachycardia, which may be sustained. Elderly patients, particularly those with compromised cardiovascular function, may be more susceptible to these effects.

Elderly patients may also be particularly susceptible to the anticholinergic effects of DENZAPINE, such as urinary retention and constipation.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindication of concomitant use
Drugs known to have a substantial potential to depress bone marrow function should not be used concurrently with DENZAPINE (see section 4.3 Contraindications). These include co-trimoxazole, chloramphenicol, sulphonamides, purazolone analgesics, phenylbutazone, penicillamine, carbamazepine or cytotoxic agents.

Long-acting depot antipsychotics (which have myelosuppressive potential) should not be used concurrently with DENZAPINE because these cannot be rapidly removed from the body in situations where this may be required, e.g. neutropenia (see section 4.3 Contraindications). Alcohol should not be used concomitantly with DENZAPINE due to possible potentiation of sedation.

Precautions including dose adjustment
DENZAPINE may enhance the central effects of CNS depressants such as narcotics, antihistamines, and benzodiazepines. Particular caution is advised when DENZAPINE therapy is initiated in patients who are receiving a benzodiazepine or any other psychotropic drug. These patients may have an increased risk of circulatory collapse, which, on rare occasions, can be profound and may lead to cardiac and/or respiratory arrest. It is not clear whether cardiac or respiratory collapse can be prevented by dose adjustment.

Because of the possibility of additive effects, caution is essential in the concomitant administration of drugs possessing anticholinergic, hypotensive, or respiratory depressant effects.

Owing to its anti-α-adrenergic properties, DENZAPINE may reduce the blood-pressure-increasing effect of norepinephrine or other predominantly α-adrenergic agents and reverse the pressor effect of epinephrine.

Concomitant administration of drugs known to inhibit the activity of some cytochrome P450 isozymes may increase the levels of clozapine, and the dose of clozapine may need to be reduced to prevent undesirable effects. This is more important for CYP 1A2 inhibitors such as caffeine (see below) and the selective serotonin reuptake inhibitors fluvoxamine and (more controversial) paroxetine. Some of the other serotonin reuptake inhibitors such as fluoxetine, paroxetine and to a lesser degree sertraline are CYP 2D6 inhibitors and, as a consequence, major pharmacokinetic interactions with clozapine are less
likely. Similarly, pharmacokinetic interactions with CYP 3A4 inhibitors such as azole antimycotics, cimetidine, erythromycin, and protease inhibitors are unlikely, although some have been reported. Because the plasma concentration of clozapine is increased by caffeine intake and decreased by nearly 50% following a 5-day caffeine-free period, dosage changes of clozapine may be necessary when there is a change in caffeine-drinking habit. In cases of sudden cessation of smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.

Cases have been reported of an interaction between citalopram and clozapine, which may increase the risk of adverse events associated with clozapine. The nature of this interaction has not been fully elucidated.

Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine, leading to reduced efficacy. Drugs known to induce the activity of cytochrome P450 enzymes and with reported interactions with clozapine include, for instance, carbamazepine (not to be used concomitantly with clozapine, due to its myelosuppressive potential), phenytoin and rifampicin. Known inducers of CYP1A2 such as omeprazole, may lead to decreased clozapine levels. The potential for reduced efficacy of clozapine should be considered when it is used in combination with these drugs.

Others
Concomitant use of lithium or other CNS-active agents may increase the risk of development of neuroleptic malignant syndrome (NMS).

Concomitant use of clozapine with drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias, including Torsades de pointes. Therefore concomitant use of these products is not recommended. Examples include certain antiarrhythmics, such as those of Class 1A(such as quinidine, disopyramide and procainamide) and Class III (such as amiodarone, sotalol and dofetilide), certain antimicrobials (sparfloxacin, moxifloxacin, erythromycin IV), tricyclic antidepressants (such as amitriptyline), certain tetracyclic antidepressants (such as maprotiline), other neuroleptics (e.g. phenothiazines, pimozide, sertindole and haloperidol), certain antihistamines (such as terfenadine), cisapride, bretylium and certain antimalarials such as quinine and mefloquine. This list is not comprehensive.

Concurrent use of drugs causing electrolyte imbalance is not recommended. Diuretics, in particular those causing hypokalemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred.

Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where DENZAPINE was co-administered with valproic acid have been reported. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.

Caution is called for in patients receiving concomitant treatment with other drugs which are either inhibitors or inducers of the cytochrome P450 isozymes. With tricyclic antidepressants, phenothiazines and type 1C anti-arrhythmics, which are known to bind to cytochrome P450 2D6, no clinically relevant interactions have been observed thus far.

An outline of drug interactions believed to be most important with DENZAPINE is given in Table 1 below (this is not an exhaustive list).

Table 1: Reference to the most common drug interactions with DENZAPINE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow suppressants (e.g. carbamazepine, chloramphenicol, sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of)</td>
<td>Interact to increase the risk and/or severity of bone marrow suppression</td>
<td>DENZAPINE should not be used concomitantly with other agents having a well known potential to suppress bone marrow function (see Section 4.3 Contraindications)</td>
</tr>
</tbody>
</table>

12
<table>
<thead>
<tr>
<th><strong>antipsychotics</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td>Concomitant use may increase risk of circulatory collapse, which may lead to cardiac and/or respiratory arrest. Whilst the occurrence is rare, caution is advised when using these drugs together. Reports suggest that respiratory depression and collapse are more likely to occur at the start of this combination or when DENZAPINE is added to an established benzodiazepine regimen.</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td>DENZAPINE potentiates the action of these drugs through additive anticholinergic activity. Observe patients for anticholinergic side-effects, e.g. constipation, especially when using to help control hypersalivation.</td>
</tr>
<tr>
<td><strong>Antihypertensives</strong></td>
<td>DENZAPINE can potentiate the hypotensive effects of these drugs due to its sympathomimetic antagonistic effects. Caution is advised if DENZAPINE is used concomitantly with antihypertensive agents. Patients should be advised of the risk of hypotension, especially during the period of initial dose titration.</td>
</tr>
<tr>
<td><strong>Alcohol, MAOIs, CNS depressants, including narcotics and benzodiazepines</strong></td>
<td>Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination with these drugs. Caution is advised if DENZAPINE is used concomitantly with other CNS active agents. Advise patients of the possible additive sedative effects and caution them not to drive or operate machinery.</td>
</tr>
<tr>
<td><strong>Highly protein bound drugs (e.g. warfarin and digoxin)</strong></td>
<td>DENZAPINE may cause an increase in plasma concentration of these drugs due to displacement from plasma proteins. Patients should be monitored for the occurrence of side effects associated with these drugs, and doses of the protein bound drug adjusted, if necessary.</td>
</tr>
<tr>
<td><strong>Phenytoin</strong></td>
<td>Addition of phenytoin to DENZAPINE drug regimen may cause a decrease in the clozapine plasma concentrations. If phenytoin must be used, the patient should be monitored closely for a worsening or recurrence of psychotic symptoms.</td>
</tr>
<tr>
<td><strong>Lithium</strong></td>
<td>Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS). Observe for signs and symptoms of NMS.</td>
</tr>
</tbody>
</table>

### 4.6 Pregnancy and lactation

**Pregnancy**

For clozapine, there are only limited clinical data on exposed pregnancies. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see 5.3). Caution should be exercised when prescribing to pregnant women.
Lactation
Animal studies suggest that clozapine is excreted in breast milk and has an effect in the nursing infant; therefore, mothers receiving DENZAPINE should not breast-feed.

Women of child-bearing potential
A return to normal menstruation may occur as a result of switching from other antipsychotics to DENZAPINE. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

4.7 Effects on ability to drive and use machines
Owing to the ability of DENZAPINE to cause sedation and lower the seizure threshold, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

4.8 Undesirable effects
For the most part, the adverse event profile of clozapine is predictable from its pharmacological properties. An important exception is its propensity to cause agranulocytosis (see section 4.4 Special warnings and precautions for use). Because of this risk, its use is restricted to treatment-resistant schizophrenia and psychosis occurring during the course of Parkinson's disease in cases where standard treatment has failed. While blood monitoring is an essential part of the care of patients receiving clozapine, the physician should be aware of other rare but serious adverse events, which may be diagnosed in the early stages only by careful observation and questioning of the patient in order to prevent morbidity and mortality.

Blood and lymphatic system
Development of granulocytopenia and agranulocytosis is a risk inherent to DENZAPINE treatment. Although generally reversible on withdrawal of treatment, agranulocytosis may result in sepsis and can prove fatal. Because immediate withdrawal of the drug is required to prevent the development of life-threatening agranulocytosis, monitoring of the WBC count is mandatory (see section 4.4 Special warnings and precautions for use). Table 2 below summarises the estimated incidence of agranulocytosis for each DENZAPINE treatment period.

Table 2: Estimated incidence of agranulocytosis

<table>
<thead>
<tr>
<th>Treatment period</th>
<th>Incidence of agranulocytosis per 100,000 person-weeks² of observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 0 - 18</td>
<td>32.0</td>
</tr>
<tr>
<td>Weeks 19 - 52</td>
<td>2.3</td>
</tr>
<tr>
<td>Weeks 53 and higher</td>
<td>1.8</td>
</tr>
</tbody>
</table>

² Person-time is the sum of individual units of time that the patients in the registry have been exposed to clozapine before experiencing agranulocytosis. For example, 100,000 person-weeks could be observed in 1,000 patients who were in the registry for 100 weeks (100*1000 = 100,000), or in 200 patients who were in the registry for 500 weeks (200*500 = 100,000) before experiencing agranulocytosis.

The cumulative incidence of agranulocytosis in the UK since monitoring began is (0 - 11.6 years between 1989 and 2001) is 0.78 %. The majority of cases (approximately 70 %) occur within the first 18 weeks of treatment.

Metabolic and Nutritional Disorders
Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. On very rare occasions, severe hyperglycaemia, sometimes leading to ketoacidosis/hyperosmolar coma, has been reported in patients on clozapine treatment with no prior history of hyperglycaemia. Glucose levels normalised in most patients after discontinuation of clozapine and in a few cases hyperglycaemia recurred when treatment was reinitiated. Although most patients had risk factors for non-insulin-dependent diabetes mellitus, hyperglycaemia has also been
Nervous System Disorders

The very common adverse events observed include drowsiness/sedation, and dizziness. DENZAPINE can cause EEG changes, including the occurrence of spike and wave complexes. It lowers the seizure threshold in a dose-dependent manner and may induce myoclonic jerks or generalised seizures. These symptoms are more likely to occur with rapid dose increases and in patients with pre-existing epilepsy. In such cases the dose should be reduced and, if necessary, anticonvulsant treatment initiated. Carbamazepine should be avoided because of its potential to depress bone marrow function, and with other anticonvulsant drugs the possibility of a pharmacokinetic interaction should be considered. In rare cases, patients treated with DENZAPINE may experience delirium.

Very rarely, tardive dyskinesia has been reported in patients on clozapine who had been treated with other antipsychotic agents. Patients in whom tardive dyskinesia developed with other antipsychotics have improved on clozapine.

Cardiac Disorders

Tachycardia and postural hypotension with or without syncope may occur, especially in the initial weeks of treatment. The prevalence and severity of hypotension is influenced by the rate and magnitude of dose titration. Circulatory collapse as a result of profound hypotension, in particular related to aggressive titration of the drug, with the possible serious consequences of cardiac or pulmonary arrest, has been reported with clozapine.

A minority of clozapine-treated patients experience ECG changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which normalise after discontinuation of clozapine. The clinical significance of these changes is unclear. However, such abnormalities have been observed in patients with myocarditis, which should therefore be considered.

Isolated cases of cardiac arrhythmias, pericarditis/pericardial effusion and myocarditis have been reported, some of which have been fatal. The majority of the cases of myocarditis occurred within the first 2 months of initiation of therapy with clozapine. Cardiomyopathy generally occurred later in the treatment.

Eosinophilia has been co-reported with some cases of myocarditis (approximately 14 %) and pericarditis/pericardial effusion; it is not known, however, whether eosinophilia is a reliable predictor of carditis.

Signs and symptoms of myocarditis or cardiomyopathy include persistent tachycardia at rest, palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea), or symptoms that mimic myocardial infarction. Other symptoms which may be present in addition to the above include flu-like symptoms. Sudden, unexplained deaths are known to occur among psychiatric patients who receive conventional antipsychotic medication but also among untreated psychiatric patients. Such deaths have been reported very rarely in patients receiving clozapine.

Vascular Disorders

Rare cases of thromboembolism have been reported.

Respiratory System

Respiratory depression or arrest has occurred very rarely, with or without circulatory collapse (see sections 4.4 Special warnings and precautions for use and 4.5 Interaction with other medicinal products and other forms of interaction).

Gastrointestinal System

Constipation and hypersalivation have been observed very frequently, and nausea and vomiting frequently. Very rarely ileus may occur (see section 4.4 Special warnings and precautions for use). Rarely DENZAPINE treatment may be associated with dysphagia. Aspiration of ingested food may occur in patients presenting with dysphagia or as a consequence of acute overdosage.
Hepatobiliary Disorders
Transient, asymptomatic elevations of liver enzymes and rarely, hepatitis and cholestatic jaundice may occur. Very rarely, fulminant hepatic necrosis has been reported. If jaundice develops, DENZAPINE should be discontinued (see section 4.4. Special warnings and precautions for use). In rare cases, acute pancreatitis has been reported.

Renal Disorders
Isolated cases of acute interstitial nephritis have been reported in association with DENZAPINE therapy.

Reproductive and Breast Disorders
Very rare reports of priapism have been received.

General Disorders
Cases of neuroleptic malignant syndrome (NMS) have been reported in patients receiving clozapine either alone or in combination with lithium or other CNS-active agents.
The table below (Table 3) summarises the adverse reactions accumulated from reports made spontaneously and during clinical studies.

Table 3: Treatment-Emergent Adverse Experience Frequency Estimate from Spontaneous and Clinical Trial Reports
Adverse reactions are ranked under headings of frequency, using the following convention: Very common (≥1/10), common (≥1/100, < 1/10), uncommon (≥1/1,000, < 1/100), rare (≥1/10,000, < 1/1,000), very rare (<1/10,000), including isolated reports.

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Leucopenia/decreased WBC/neutropenia, eosinophilia,</td>
</tr>
<tr>
<td>leukocytosis</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Anaemia</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Thrombocythaemia</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Weight gain</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Impaired glucose tolerance, diabetes mellitus</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Ketoacidosis, hyperosmolar coma, severe hyperglycaemia,</td>
</tr>
<tr>
<td>hypertriglyceridaemia, hypercholesterolaemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Restlessness, agitation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
</tr>
<tr>
<td>Drowsiness/sedation, dizziness</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Blurred vision, headache, tremor, rigidity, akathisia,</td>
</tr>
<tr>
<td>extra pyramidal symptoms,</td>
</tr>
<tr>
<td>Disorder</td>
</tr>
<tr>
<td>----------------------------------</td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
</tr>
<tr>
<td>Very common</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td><strong>Respiratory disorders</strong></td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
</tr>
<tr>
<td>Very common</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
</tr>
<tr>
<td>Very rare</td>
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Renal and urinary disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Urinary incontinence, urinary retention</td>
</tr>
<tr>
<td>Very rare</td>
<td>Interstitial nephritis</td>
</tr>
</tbody>
</table>

Reproductive system disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Priapism</td>
</tr>
</tbody>
</table>

General disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>Very rare</td>
<td>Sudden unexplained death</td>
</tr>
</tbody>
</table>

Investigations

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Increased CPK</td>
</tr>
</tbody>
</table>

4.9 Overdose

In cases of acute intentional or accidental clozapine overdosage for which information on the outcome is available, mortality to date is about 12%. Most of the fatalities were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses above 2000 mg. There have been reports of patients recovering from an overdose in excess of 10,000 mg. However, in a few adult individuals, primarily those not previously exposed to clozapine, the ingestion of doses as low as 400 mg led to life-threatening comatose conditions and, in one case, to death. In young children, the intake of 50 to 200 mg resulted in strong sedation or coma without being lethal.

Signs and symptoms

Drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extra pyramidal symptoms, hyperreflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, respiratory depression or failure.

Treatment

Gastric lavage and/or administration of activated charcoal within the first 6 hours after the ingestion of the drug. Peritoneal dialysis and haemodialysis are unlikely to be effective. Symptomatic treatment under continuous cardiac monitoring, surveillance of respiration, monitoring of electrolytes and acid-base balance. The use of epinephrine should be avoided in the treatment of hypotension because of the possibility of a 'reverse epinephrine' effect. Close medical supervision is necessary for at least 5 days because of the possibility of delayed reactions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotic agent (ATC code NO5A H02)
Clozapine has been shown to be an antipsychotic agent that is different from classic antipsychotics.

In pharmacological experiments, the compound does not induce catalepsy or inhibit apomorphine- or amphetamine-induced stereotyped behaviour. It has only weak dopamine-receptor-blocking activity at D₁, D₂, D₃ and D₄ receptors, but shows high potency for the D₄ receptor, in addition to potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal-reaction-inhibiting effects. It has also been shown to possess antiserotonergic properties.
Clinically, clozapine produces rapid and marked sedation and exerts antipsychotic effects in schizophrenic patients resistant to other drug treatment. In such cases, clozapine has proven effective in relieving both positive and negative schizophrenic symptoms mainly in short-term trials. In an open clinical trial performed in 319 treatment resistant patients treated for 12 months, a clinically relevant improvement was observed in 37% of patients within the first week of treatment and in an additional 44% by the end of 12 months. The improvement was defined as about 20% reduction from baseline in Brief Psychiatric Rating Scale Score. In addition, improvement in some aspects of cognitive dysfunction has been described.

Compared to classic antipsychotics, clozapine produces fewer major extra pyramidal reactions such as acute dystonia, parkinsonian-like side effects and akathisia. In contrast to classic antipsychotics, clozapine produces little or no prolactin elevation, thus avoiding adverse effects such as gynaecomastia, amenorrhoea, galactorrhoea, and impotence.

A potentially serious adverse reaction caused by clozapine therapy is granulocytopenia and agranulocytosis occurring at an estimated incidence of 3% and 0.7%, respectively. In view of this risk, the use of DENZAPINE should be limited to patients who are treatment-resistant or patients with psychosis in Parkinson's disease when other treatment strategies have failed (see section 4.1 Therapeutic indications) and in whom regular haematological examinations can be performed (see sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

5.2 Pharmacokinetic properties

The absorption of orally administered DENZAPINE is 90 to 95%; neither the rate nor the extent of absorption is influenced by food.

Clozapine is subject to moderate first-pass metabolism, resulting in an absolute bioavailability of 50 to 60%. In steady-state conditions, when given twice daily, peak blood levels occur on an average at 2.1 hours (range: 0.4 to 4.2 hours), and the volume of distribution is 1.6 l/kg. Clozapine is approximately 95% bound to plasma proteins. Its elimination is biphasic, with a mean terminal half-life of 12 hours (range: 6 to 26 hours). After single doses of 75 mg the mean terminal half-life was 7.9 hours; it increased to 14.2 hours when steady-state conditions were reached by administering daily doses of 75 mg for at least 7 days. Dosage increases from 37.5 mg to 75 mg and 150 mg given twice daily were found to result during steady state in linearly dose-proportional increases in the area under the plasma concentration/time curve (AUC), and in the peak and minimum plasma concentrations.

Clozapine is almost completely metabolised before excretion. Of the main metabolites only the demethyl metabolite was found to be active. Its pharmacological actions resemble those of clozapine, but are considerably weaker and of short duration. Only trace amounts of unchanged drug are detected in the urine and faeces, approximately 50% of the administered dose being excreted as metabolites in the urine and 30% in the faeces.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential (for reproductive toxicity, see section 4.6). There are no preclinical data of any relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Microcrystalline cellulose
- Lactose monohydrate
- Povidone
- Sodium Starch Glycolate (Type A)
- Magnesium Stearate

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
6.3 **Shelf life**
Blister packs 4 years
HDPE bottles 4 years

6.4 **Special precautions for storage**
Do not store above 30°C. Store in the original packaging. Keep in the outer carton to protect from light.

6.5 **Nature and contents of container**
Transparent PVC/PVDC/PE/ Aluminium Foil Blister Strips in a cardboard carton containing 20, 50 or 100 tablets.

HDPE bottles with polypropylene child-resistant, tamper-evident cap containing 50 & 100 tablets.

**Pack sizes for 20286/0012:**

Transparent PVC/PVDC/PE/ Aluminium Foil Blister Strips in a cardboard carton containing 20 or 50 tablets.

HDPE bottles with polypropylene child-resistant, tamper-evident cap containing 50 tablets.

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

7 **MARKETING AUTHORISATION HOLDER**
Merz Pharma UK Ltd
260 Centennial Park
Elstree, Herts
WD6 3SR
UK

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 20286/0011
PL 20286/0012

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
16/02/2009

10 **DATE OF REVISION OF THE TEXT**
16/02/2009
Module 3

Product Information Leaflet

DENZAPINE® 25, 50, 100 AND 200 mg TABLETS
CLOZAPINE

PACKAGE LEAFLET – INFORMATION FOR THE USER

The use of DENZAPINE is restricted to those patients registered with the Denzapine Monitoring Service.

Read all of this leaflet carefully before you start taking this medicine.
Keep this leaflet. You may need to read it again.
If you have any further questions, please ask your doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet
1. What DENZAPINE is and what it is used for
2. Before you take DENZAPINE
3. How to take DENZAPINE
4. Possible side effects
5. How to store DENZAPINE
6. Further information

1. WHAT DENZAPINE IS AND WHAT IT IS USED FOR

DENZAPINE contains clozapine, which belongs to a group of medicines called atypical antipsychotics. Antipsychotics are mainly used to treat schizophrenia. Schizophrenia is a psychiatric disorder that affects the way a person thinks and behaves.

DENZAPINE is used:
- to treat schizophrenia when other antipsychotic medicines have not worked or have caused severe side effects
- to treat psychotic disorders occurring in patients with Parkinson's disease, when standard treatment has failed

DENZAPINE is available only with a doctor's prescription. Ask your doctor if you have any questions about why this medicine has been prescribed for you.
2. BEFORE YOU TAKE DENZAPINE

DENZAPINE must not be given to anyone who is unconscious or in coma.

Do NOT take DENZAPINE if:
- you are allergic (hypersensitive) to clozapine or to any of the other ingredients of the DENZAPINE tablets (see section 6, "Further information"). It is important to tell your doctor if you think you have ever had an allergic reaction to any of these ingredients.
- Symptoms of an allergic reaction can include:
  - swelling of the face and mouth
  - itchy skin rashes or hives
  - difficulty breathing
  - faintness
- if you are unable to digest lactose (milk sugar), due to one of the following conditions:
  - galactose intolerance
  - lactase deficiency
  - glucose-galactose malabsorption
- you are unable to undergo regular blood tests
- you have a low number of white cells in the blood (granulocytopenia/agranulocytosis)
- you have ever had a low white blood cell count that was unexplained or was caused by medical treatment (except antitumour treatment)
- you are receiving treatment with other medicines that can cause a fall in the number of white blood cells
- you have suffered from a very low white blood cell count (agranulocytosis) caused by previous treatment with DENZAPINE.

You have any of the following diseases:
- disorders of the bone marrow (when the bone marrow does not make enough blood cells)
- uncontrolled epilepsy (fits or seizure)
- acute mental illness caused by alcohol, medicines or other substances
- poisoning caused by other medicines
- circulatory collapse (a very pronounced fall in blood pressure that may lead to unconsciousness)
- disorders affecting the brain that can lead to drawniness or unconsciousness
- severe kidney disease
- heart disease (such as myocarditis, pericarditis or cardiomyopathy)
- active liver disease with jaundice (yellow colouration of the skin and eyes), feeling sick and loss of appetite
- liver failure (very serious liver disease)
- paralytic ileus (a disorder of the small intestines)

Take special care with DENZAPINE

Please tell your doctor if you have or have had any medical conditions or illnesses, especially the following:
- low number of white blood cells (leukopenia, neutropenia, granulocytopenia, agranulocytosis)
- high number of a certain type of white blood cells called eosinophil granulocytes (eosinophilia)
- low number of platelets in the blood (thrombocytopenia)
- pericarditis or pericardial effusion (inflammation of the membranes around the heart)
- if you or any member of your family have changes on the heart trace (ECG)
- orthostatic hypotension (a fall in blood pressure on standing up)
- epilepsy or fits, even if they are well controlled
- liver disease
- enlargement of the prostate
- glaucoma (raised pressure in the eye)
- constipation, paralytic ileus, disease of the large bowel or operations on the abdomen
PAR Denzapine 50mg & 200mg tablets

- fever
- Neuroleptic Malignant Syndrome, a serious reaction to some anti-psychotic medicines. Symptoms include a sudden increase in body temperature, sweating, a fast heart beat, muscle stiffness and a fluctuating blood pressure. It can lead to coma.
- diabetes
- stroke
- blood clots in your veins (thromboembolism). If you are not mobile you are at increased risk of developing blood clots while taking DENZAPINE

Also tell your doctor if you are taking any other antipsychotic medicines (see section "Taking other medicines" below).

DENZAPINE may lower the number of your white blood cells, making you more prone to infections. Before and during your treatment with DENZAPINE, your doctor will monitor your blood count closely to make sure that the number of your white blood cells do not fall under a certain level. Please tell your doctor if you develop any signs of infection, such as fever, sore throat or flu-like symptoms.

If this medicine makes you feel dizzy, light-headed or faint, be careful when getting up from a sitting or lying position. DENZAPINE may lower your blood pressure, especially at the start of treatment. These symptoms can usually be prevented by getting up slowly and flexing leg muscles and toes to get the blood circulating. When getting out of bed, dangle your legs over the side for a minute or two before standing up.

Be careful when drinking alcohol or when taking antihistamines (medicines used for hay fever, allergies or colds), sleeping tablets or tablets to relieve pain while taking this medicine. DENZAPINE can increase drowsiness caused by alcohol and by medicines affecting your nervous system.

DENZAPINE may affect the way your body controls temperature, and it may prevent sweating even in very hot weather. Exercise, hot baths or saunas may make you feel dizzy or faint while you are taking this medicine.

Taking other medicines

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

Some medicines must NOT be used when you are taking DENZAPINE. These include:
- medicines that affect the bone marrow. These can decrease the number of blood cells produced by the bone marrow. They include:
  - some antibiotics (e.g. co-trimoxazole, chloramphenicol, sulphonamides)
  - certain pain-killers (e.g. phenylbutazone, oxybutazone, antipyrine, dipyrone)
  - penicillamine (for rheumatoid arthritis)
  - carbamazepine (for epilepsy and for neuralgic pain)
  - cytotoxic (anticancer) medicines
  - other antipsychotic medicines (neuroleptics), especially when given as a depot (for long-term treatment)

Other medicines can be affected by DENZAPINE or may affect how well DENZAPINE works. Your doctor will tell you what medicines you can take and their doses. Please also consult your doctor if you are taking any of the medicines listed below:
- medicines that can make you drowsy e.g. morphine (for pain), benzodiazepines (sleeping pills) and antihistamines (for allergies) such as loratadine, chlorpheniramine
- anticholinergic medicine, which are used to relieve stomach cramps, spasms and travel sickness
- medicines used to treat high blood pressure, e.g. metoprolol, captopril, enalapril

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medicines used to treat a fast or irregular heart beat
(antiarrhythmics, e.g. flecainide, pilsicainide)
- medicines that can cause changes on the heart trace (ECG). Your
doctor will know which medicines these are
- medicines that can cause constipation, particularly certain
medicines to treat psychosis, depression or Parkinson’s disease.
Your doctor will know which medicines these are
- atropine, a medicine which may be used in some eye drops or
cough preparations
- medicines which may cause excessive salt loss, such as diuretics
(water tablets)
- adrenaline (epinephrine), a medicine used in emergency situations
- warfarin, a medicine to prevent blood clots
- digoxin (for heart diseases)
- cimetidine, used for stomach ulcers
- erythromycin and rifampicin (antibiotics)
- medicines to treat fungal infections, such as ketoconazole,
itraconazole and micazole
- medicines to treat epilepsy e.g. phenytoin, carbamazepine, valproic
acid
- medicines for depression, such as fluoxetine, fluoxetine,
paroxetine, sertraline, citalopram, amitriptyline, phenelzine,
moclobemide, chlorpromazine, mirtazapine or tianeptine
- lithium (for mental disorders)
- medicines which affect how your body eliminates clonazepam. Your
doctor will know which medicines these are
- omeprazole (a drug used to treat excess stomach acid)

Your doctor and pharmacist have more information on medicines to be
careful with or avoid while taking DENZAPINE.

Taking DENZAPINE with food and drink
You can take your DENZAPINE tablets with or without food.
DENZAPINE may increase the effect of alcohol. Therefore, you should
not drink alcohol during treatment.
Coffee can affect the levels of clonazepam (the active substance of
DENZAPINE) in your blood. You may drink coffee. However, if you stop
drinking coffee suddenly, the levels of clonazepam in your blood may fall.
This will make the medicine less effective. Equally, if you start drinking
coffee, the levels may rise, increasing the risk of side effects.

Smoking
Smoking can affect the levels of clonazepam in your blood. If you stop
smoking suddenly, the levels of clonazepam in your blood may rise. This
may increase the risk of side effects.

Children
DENZAPINE is not recommended for use in children.

Pregnancy
Tell your doctor if you are or think you may be pregnant or if you are
planning to become pregnant.
There is limited information on the safety of DENZAPINE tablets in
pregnancy. Your doctor will discuss with you the risks and benefits of
taking this medicine during pregnancy.
Some women taking antipsychotic medicines have irregular or no
periods. If you have been affected in this way, your periods may return
when your medication is changed to DENZAPINE. In these
circumstances you should be sure to take adequate contraceptive
precautions.

Breast-feeding
If you are breast-feeding, DENZAPINE can reach your baby through
your breast milk. DENZAPINE should not be used when breast-feeding.

Driving and using machines
You may feel tired, drowsy, dizzy or you may feel faint while taking
DENZAPINE, especially during the early stages of treatment. If you
have any of these symptoms, do not drive, operate machinery or do
any tasks where you need to be alert.
PAR Denzapine 50mg & 200mg tablets
PL. 20286/0011-0012; UK/H/1463/01-02/DC

3. HOW TO TAKE DENZAPINE

Your dose of DENZAPINE has been determined by your doctor. The dose will depend on how well you respond to the medicine. It will also depend on the other medicines you are taking and other medical conditions you may have. The dose may be altered from time to time.

Carefully follow all the instructions given to you by your doctor and pharmacist. Their instructions may differ from the information contained in this leaflet. If you do not understand the instructions on the label, ask your doctor or pharmacist for help. Take DENZAPINE exactly as prescribed by your doctor to prevent unwanted side effects.

Do not take more or less DENZAPINE than your doctor has prescribed. If you think the dose is too weak or too strong, talk to your doctor.

Dosage

The total amount of DENZAPINE you take each day is usually divided into two doses. If you have to divide your dose, you should take the larger dose at bedtime. However, if your total daily dose is not over 200 mg, it is not necessary to divide the dose. In this case, it is usually taken in the evening.

Swallow DENZAPINE tablets with a full glass of water or other liquid. Taking the tablets at the same time each day will have the best effect and will help you remember to take them.

Schizophrenic patients resistant to other treatments

When you first start taking DENZAPINE, the usual dose is half a 25 mg tablet (12.5 mg) taken once or twice on the first day, followed by one or two 25 mg tablets taken on the second day. If this dose is well tolerated, it may be increased gradually, usually to between 200 mg and 450 mg per day.

However, some people may need a higher dose. The maximum permissible dose is 900 mg per day. Once the maximum benefit is achieved, your doctor may reduce the dose gradually to a lower level. Your doctor will determine the most appropriate dose for you.

Parkinsonian patients with psychiatric disorders who do not respond to standard treatment

The initial dose is of 12.5 mg (half a 25 mg tablet) taken in the evening. The dose is gradually increased to a maximum of 50 mg per day, taken in the evening. The effective dose is usually between 25 mg and 37.5 mg (one to one-and-a-half 25 mg tablets). If the 50 mg dose is not effective, it can be increased to 100 mg in some patients. This dose (100 mg) must not be exceeded.

Elderly patients

DENZAPINE tablets can be used in the elderly (over 65 years of age). Treatment usually begins with a lower dose (e.g. 12.5 mg daily), which is then gradually increased.

Duration of treatment

You should take DENZAPINE for at least 6 months. Do not stop taking this medicine without first talking to your doctor.

If you have heart, kidney or liver disease, epilepsy or are elderly, or if you are taking any other medicines that may affect the way DENZAPINE works, your doctor may start you on a lower dose to prevent unwanted effects. The dose will be increased slowly.

WHILE TAKING DENZAPINE

Tell all of the doctors and pharmacists who are treating you that you are taking DENZAPINE.

You must have regular blood tests while taking DENZAPINE.

Blood tests

Before starting DENZAPINE you will have a blood test to make sure that you can take this medicine.

DENZAPINE can cause agranulocytosis. In this condition, the number of white blood cells (which are necessary for fighting infection) is too low. If this occurs, you are at risk of suffering infections which may be life-threatening. Warning signs include flu-like symptoms, a sore throat or fever. If you develop these or any other signs suggestive of infection, you should contact your doctor immediately.

There is no way of knowing who is at risk of developing agranulocytosis. Deaths have occurred in severe cases of agranulocytosis, although with regular blood tests, agranulocytosis can be detected early. If DENZAPINE is stopped as soon as a problem is detected, the white blood cell numbers should return to normal. You must understand the importance of regular blood tests by your doctor while taking DENZAPINE.

After starting treatment with DENZAPINE, you will have a blood test once a week for the first 10 weeks. The risk of agranulocytosis is highest in this period. For the rest of the first year of treatment, blood tests will be performed every 2 weeks. After the first year, tests will be performed every 4 weeks for as long as you continue to take DENZAPINE. Tests will also be performed for one month after stopping the medicine. These tests will tell the doctor if there is any problem with the number of white cells in your blood. There are some situations where you may need to have blood tests more often (e.g. twice a week). Your doctor will talk to you about this.

If the number of your white blood cells falls below a critical level, DENZAPINE must be stopped immediately and you must never take any medicines containing clozapine again.

Things which I must not do:

- do not stop taking DENZAPINE or lower the dose even if you are feeling better, unless your doctor tells you to do so. Your condition may worsen if you suddenly stop taking it. Your doctor will gradually reduce the amount you take each day before stopping the medicine completely.
- do not give DENZAPINE to anyone else even if they have the same symptoms as you. It may harm them even if their condition seems similar to yours.

When changing from a previous antipsychotic treatment to DENZAPINE, the first treatment should be gradually withdrawn before starting DENZAPINE.

- Continued over the page -

- do not use DENZAPINE to treat other complaints unless your doctor tells you to.

If you take more DENZAPINE than you should

If you suspect that you or someone else has taken too many DENZAPINE tablets, contact a doctor immediately or go to the Accident and Emergency Department at your nearest hospital. Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention. Keep the telephone numbers for these places handy.

The most common signs and symptoms of overdose include:

- drowsiness
- confusion and coma
- delirium
- agitation
- light-headedness
- a fall in blood pressure
- collapse
- shallow or slow breathing or sometimes shortness of breath
- fast or irregular heartbeat
- dribbling
- fits

If you forget to take DENZAPINE

If it is almost time for your next dose (within four hours), forget the dose you missed and take your next dose at its normal time. Otherwise take it as soon as you remember, and then go back to taking your tablets as you would normally.

If you miss a dose of DENZAPINE do not take a double dose to make up for the missed dose.

If you have stopped taking DENZAPINE for more than two days, you must contact your doctor before starting to take it again. In this case, the medicine must be started again at a low dose and then increased.

If you have trouble remembering to take your medicine, ask your pharmacist for some hints.

If your doctor tells you to stop taking DENZAPINE

If the medicine needs to be stopped abruptly due to side effects, you will be monitored closely for psychiatric symptoms. Other symptoms can also arise, including increased sweating, headache, nausea (feeling sick), vomiting and diarrhoea.
4. POSSIBLE SIDE EFFECTS

Like all medicines, DENZAPINE can cause side effects although not everybody gets them. The frequency of side effects is based on the following:

| Very common: | In more than 1 in 10 patients treated |
| Common: | In less than 1 in 10, but more than 1 in 100 patients treated |
| Uncommon: | In less than 1 in 100, but more than 1 in 1,000 patients treated |
| Rare: | In less than 1 in 1,000, but more than 1 in 10,000 patients treated |
| Very rare: | In less than 1 in 10,000 patients treated, including single reports |

The following side effects have been associated with DENZAPINE:

**Very common:**
- Drowsiness
- Dizziness
- A fast heart beat (tachycardia)
- Constipation
- Hyperactivity (forming a large volume of saliva)

**Common:**
- A fall in the number of white cells in the blood (leukopenia, neutropenia, granulocytopenia, agranulocytosis) (see Section 3, “How to take DENZAPINE”)
- Eosinophilia (an increase in the number of a certain type of white blood cells called eosinophil granulocytes)
- Leukocytosis (an increase in the number of white blood cells)
- Weight gain
- Blurred vision
- Headache
- Tremor
- Stiffness of the limbs (rigidity)
- Restlessness (akathisia)

**Problems of coordination**
- Epileptic fits (localised or generalised)
- Changes on the heart trace (ECG)
- High blood pressure (hypertension)
- A fall in the blood pressure on standing up (orthostatic hypotension)
- Fainting
- Nausea (feeling sick)
- Vomiting
- Loss of appetite (anorexia)
- Dry mouth
- Changes in the blood tests that assess how the liver is working
- Urinary incontinence
- Urinary retention (the inability to pass urine)
- Fatigue
- Fever
- Benign hyperpyrexia (drug fever; changes in body temperature caused by certain medicines)
- Alterations in the body’s control of temperature
- Alterations of sweating

**Uncommon:**
- Agranulocytosis (a very low number of white cells in the blood)
- Neuroleptic malignant syndrome (fever, sweating, a fast heart beat, muscle stiffness and changes in blood pressure)

**Rare:**
- Impaired glucose tolerance (excess sugar levels in the blood)
- Diabetes mellitus
- Restlessness (agitation)
- Confusion
- Delirium
- Circulatory collapse (a very low blood pressure that can lead to unconsciousness)
- Irregular heart beat (arrhythmia)
- Ventricular arrhythmias (life-threatening disorders of the heart. These are medical emergencies.)
- Inflammation of the heart muscle (myocarditis)

**Very rare:**
- A fall in the number of platelets in the blood (thrombocytopenia)
- Complications of excessive sugar in the blood (severe hyperglycaemia, ketocidosis, hyperosmolar coma)
- Excessive fat in the blood (hypertriglyceridaemia)
- Tardive dyskinesia (slow, abnormal movements of the face, tongue and lips)
- Disease of the heart muscle (cardiomyopathy)
- Cardiac arrest
- Torsades de pointes (a life-threatening disorder of the heart. This is a medical emergency.)
- Very slow or shallow breathing (respiratory depression)
- Absence of breathing (respiratory arrest)
- Enlargement of the parotid glands (salivary glands)
- Abnormal bowel movement (intestinal obstruction, paralytic ileus, faecal impaction)
- Death of the liver (fulminant hepatic necrosis)
- Skin reactions
- Inflammation of the kidney (interstitial nephritis)
- A persistent and possibly painful erection (priapism)
- Sudden unexplained death

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
5. HOW TO STORE DENZAPINE

Keep DENZAPINE out of the reach and sight of children. A locked cupboard at least one and a half metres from the ground is a good place to store medicines.

Do not take DENZAPINE after the expiry date shown on the outer carton or on the blister strip. The expiry date refers to the last day of that month.

Do not take DENZAPINE if the packaging is damaged or shows signs of tampering.

Do not store above 30°C. Store in the original packaging. Keep in the outer carton to protect from light.

Keep your tablets in the original container until it is time to take them.

Do not store DENZAPINE or any medicine in the bathroom or near a sink.

Do not leave it in a car or on a window sill. Heat and dampness can destroy medicines. If your tablets appear to change in their appearance or show any other apparent signs of deterioration, do not take the tablets but refer immediately to the pharmacist.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What DENZAPINE contains
- The active substance is clozapine
  - One DENZAPINE 25 mg tablet contains 25 mg clozapine.
  - One DENZAPINE 50 mg tablet contains 50 mg clozapine.
  - One DENZAPINE 100 mg tablet contains 100 mg clozapine.
  - One DENZAPINE 200 mg tablet contains 200 mg clozapine.
- The other ingredients are:
  - microcrystalline cellulose
  - lactose monohydrate
  - povidone
  - sodium starch glycolate
  - magnesium stearate

What DENZAPINE looks like and contents of the pack
DENZAPINE 25 mg tablets are small, round, yellow tablets with “25” embossed over a breakline on one face, the other side is plain.
DENZAPINE 50 mg tablets are small, round, yellow tablets with “50” embossed over a breakline on one face, the other side is plain.
DENZAPINE 100 mg tablets are small, round, yellow tablets with “100” embossed over a breakline on one face, the other side is plain.
DENZAPINE 200 mg tablets are large, oval shaped, yellow tablets with “200” on one side and a breakline on the other side.
The breakline allows the tablet to be broken for easier swallowing.
DENZAPINE 25 and 100 mg tablets are supplied in bottles of 100 tablets and in blister packs containing 28 or 84 tablets.
DENZAPINE 50 mg tablets are supplied in bottles of 100 tablets and in blister packs containing 20 or 50 tablets.
DENZAPINE 200 mg tablets are supplied in blister packs containing 50 tablets.
The quantity provided to you by the pharmacy will be determined by your doctor.

The Marketing Authorisation holder and manufacturer:
Merz Pharma UK Ltd
Unit 280 Centennial Park, Elstree Hill South
Elstree, Herts, WD6 3SR, UK

If you have any further questions about your medicine or are unsure about any of the advice in this leaflet, ask your doctor or pharmacist.

Marketing Authorisation number:
DENZAPINE 25 mg tablets PL 20286/0001 (PA 1438/1/1)
DENZAPINE 50 mg tablets PL 20286/0011 (PA 1438/1/3)
DENZAPINE 100 mg tablets PL 20286/0002 (PA 1438/1/2)
DENZAPINE 200 mg tablets PL 20286/0012 (PA 1438/1/4)

This leaflet was last approved in January 2009.
Module 4

Labelling

Denzapine 50mg tablets

Blister carton - pack size 50 tablets
Denzapine 200mg tablets

Blister carton - pack size 50 tablets
Blister foils

Denzapine 50mg tablets
Denzapine 200mg tablets
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 Marketing Authorisations for the medicinal products Denzapine 50mg and 200mg tablets (PL 20286/0011-0012, UK/H/1463/01-02/DC) on 16th February 2009. The products are prescription-only medicines.

These are abridged applications for Denzapine 50mg and 200mg tablets, two strengths of clozapine, submitted under Article 10.3 of 2001/83 EC, as amended. The applications refer 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 Tablets contain 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 applications cross-refer 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, Clozapine 12.5mg Tablets (half a Clozapine 25mg Tablet), 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 these products. 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 tablets  
Denzapine 200mg tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Name(s) of the active substance(s) (INN)</strong></td>
<td>Clozapine</td>
</tr>
<tr>
<td><strong>Pharmacotherapeutic classification (ATC code)</strong></td>
<td>Antipsychotic agent (N05A H02)</td>
</tr>
<tr>
<td><strong>Pharmaceutical form and strength(s)</strong></td>
<td>Tablets – 50mg &amp; 200mg</td>
</tr>
<tr>
<td><strong>Reference numbers for the Mutual Recognition Procedure</strong></td>
<td>UK/H/1463/01-02/DC</td>
</tr>
<tr>
<td><strong>Reference Member State</strong></td>
<td>United Kingdom</td>
</tr>
<tr>
<td><strong>Member States concerned</strong></td>
<td>Ireland</td>
</tr>
<tr>
<td><strong>Marketing Authorisation Number(s)</strong></td>
<td>PL 20286/0011-0012</td>
</tr>
</tbody>
</table>
| **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-methyl)piperazin-1-yl)-5H-dibenzo[b,e][1,4]diazepine

Structure:

Molecular formula: $\text{C}_{18}\text{H}_{19}\text{ClN}_4$
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 50mg tablets are presented as round, yellow, bevel-edged tablets, embossed with ‘50’ over a pressure sensitive breakline on one face. The 200mg tablets are presented as, oval-shaped, yellow tablets, embossed with ‘200’ on one face, and a breakline on the other.

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, povidone, sodium starch glycolate, magnesium stearate, and microcrystalline cellulose. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

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

There were no novel excipients used and no overages.

**Dissolution and impurity profiles**

Comparative dissolution and impurity data were provided for both strengths of the generic clozapine tablets and suitable reference (innovator) products. The dissolution and impurity profiles were found to be similar, with all impurities within the specification limits.

**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 specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished products. 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 specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

Two types of primary packaging are licensed for marketing of the finished products:

1. polyvinylchloride (PVC) / polyethylene (PE) / polyvinylidene chloride (PVDC) / aluminium foil blister strips
2. HDPE containers with polypropylene child-resistant, tamper evident closures
The capsules are packed in the blisters / HDPE containers, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The 50mg strength tablets are packaged in blister pack sizes of 20, 50 and 100, and in HDPE container pack sizes of 50 and 100, and the 250mg strength tablets are packaged in blister pack sizes of 20 and 50, and in HDPE container pack sizes of 50.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All 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 4 years has been set for both the blister packs and HDPE bottles; this is satisfactory. Storage conditions are ‘Do not store above 30°C. Store in the original packaging. Keep in the outer carton to protect from light’.

**Bioequivalence Study**

A bioequivalence study was presented comparing the test product, Clozapine 12.5mg Tablets (half a Clozapine 25mg Tablet), 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 SmPCs, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling fulfils the statutory requirements for Braille.

**Conclusion**

Considering the bioequivalence, and other quality, data provided, Clozapine 12.5mg Tablets has been shown to be a generic medicinal product of Clozaril Tablets 12.5mg. The results of the bioequivalence study were extrapolated to the 50mg and 200mg strength tablets.

As Clozapine 25mg, 50mg, 100mg and 200mg Tablets meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 12.5mg strength were extrapolated to the 50mg and 200mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. Marketing Authorisations were, therefore, granted.
III.2 PRE-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for these applications for hybrid versions 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 SmPCs.

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 Clozapine 12.5mg Tablets (test) - half a Clozapine 25mg Tablet, and Clozaril Tablets 12.5mg - half a Clozaril Tablets 25mg, 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. The low strength of Clozapine 12.5mg Tablets (half a Clozapine 25mg Tablet) 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 subjects under fasting conditions. The study was carried out using half tablets broken by hand (12.5 mg). A single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 5 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 HPLC/MS/MS method.

The primary pharmacokinetic parameters for this study were $C_{\text{max}}$, AUC_{0-\text{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 $C_{\text{max}}$, AUC_{0-\text{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: 5 days. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD) – Clozapine

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-\text{t}} xg/ml/h</th>
<th>AUC_{0-\infty} xg/ml/h</th>
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<tr>
<td>Test</td>
<td>247.95 ± 89.92</td>
<td>261.59 ± 94.21</td>
<td>26.12 ± 9.24</td>
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<tr>
<td>Reference</td>
<td>268.43 ± 113.13</td>
<td>281.41 ± 119.13</td>
<td>29.32 ± 9.67</td>
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<tr>
<td>90% CI of T/R Ratio</td>
<td>0.88 – 1.04</td>
<td>0.89 – 1.04</td>
<td>0.83 – 0.95</td>
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</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-\text{t}} xg/ml/h</th>
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<tr>
<td>Test</td>
<td>130.79 ± 34.79</td>
<td>153.63 ± 50.83</td>
<td>7.05 ± 2.45</td>
</tr>
<tr>
<td>Reference</td>
<td>136.50 ± 38.61</td>
<td>160.46 ± 59.66</td>
<td>7.40 ± 2.07</td>
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<tr>
<td>90% CI of T/R Ratio</td>
<td>0.912 – 1.012</td>
<td>0.908 – 1.024</td>
<td>0.86 – 1.03</td>
</tr>
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</table>

### 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 $C_{\text{max}}$, AUC_{0-\text{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 half tablets of the 25mg test and reference products has been shown.

Satisfactory justification is provided for a bio-waiver for Clozapine 50mg and 200mg Tablets. As Clozapine 25mg, 50mg, 100mg and 200mg Tablets meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 12.5mg strength were extrapolated to the 50mg and 200mg strength tablets.
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 approved SmPCs are consistent with those for the reference products, and are acceptable.

Patient Information Leaflet
The final PIL is in line with the approved SmPCs 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 (Clozapine 12.5mg Tablets) and reference (Clozaril Tablets 12.5mg: half a Clozaril Tablet 25mg - PL 00101/0228, Novartis Pharmaceuticals UK Limited) products within general acceptance limits. The results and conclusions of the bioequivalence study on the 12.5mg strength were extrapolated to the 50mg and 200mg strength products.

Sufficient clinical information has been submitted to support these applications. Marketing Authorisations were, therefore, granted on medical grounds.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Denzapine 50mg and 200mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

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

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Clozapine 12.5mg Tablets, and the reference product, Clozaril Tablets 12.5mg (half a Clozaril Tablet 25mg - PL 00101/0228, Novartis Pharmaceuticals UK Limited).

As Clozapine 25mg, 50mg, 100mg and 200mg Tablets meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 12.5mg strength were extrapolated to the 50mg and 200mg strength tablets, and no separate bioequivalence studies were necessary.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

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. The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before those pack sizes are commercially marketed.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study and the valid extrapolation of its results and conclusions support the claim that the applicant’s Denzapine 50mg and 200mg Tablets are hybrid versions of 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

There have been no variation applications submitted after approval of the initial procedure.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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