Summary of Product Characteristics

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

As a consequence of a European regulatory initiative, the Denzapine Summary of Product Characteristics (SmPC) has been harmonised across Europe. Blood monitoring should be carried out in accordance with national-specific official recommendations.

The Denzapine Monitoring Service (DMS) was developed in order to manage the risk of agranulocytosis associated with clozapine. It is available 24 hours a day. When a monitoring service is not used, evidence suggests a mortality rate from agranulocytosis of 0.3%[1]. This is compared to a mortality rate when clozapine is used in conjunction with a Monitoring Service, of 0.01%[2].

The Denzapine Monitoring Service provides centralised monitoring of neutrophil counts which is a mandatory requirement for all patients in Ireland who are treated with Denzapine. The use of Denzapine is restricted to patients who are registered with the Denzapine Monitoring Service. In addition to registering their patients, prescribing physicians must register themselves and a nominated pharmacist with the Denzapine Monitoring Service. All Denzapine-treated patients must be under the supervision of an appropriate specialist and supply of Denzapine is restricted to hospital and retail pharmacies registered with the Denzapine Monitoring Service. Denzapine is not sold to, or distributed through wholesalers.

If the blood result of a patient taking Denzapine is below the normal range (See Section 4.4), Clonmel Healthcare Ltd. will contact the physician and pharmacist registered to the patient on the Denzapine Monitoring Service to inform them.

The Denzapine Monitoring Service maintains a database which includes all patients who have developed abnormal neutrophil findings and who should not be re-exposed to Denzapine or any other brand of clozapine.

Prescribers and pharmacists should adhere to brand prescribing and dispensing of clozapine in order to prevent the disruption to effective monitoring that may be caused if patients switch brands.

Furthermore, in order to protect patient safety, at any one time patients should only be prescribed one brand of clozapine and only registered with the monitoring service connected to that brand.

For further information regarding Denzapine and the Denzapine Monitoring Service please call **1800 936 081** (Ireland).

[1] De la Chapelle A, et al. *Clozapine-induced agranulocytosis: a genetic and epidemiologic study*. Hum Genet, 1977. 37: p. 183-194.

[2] Denzapine Monitoring Service, data on file.

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 section 4.1)**
- **who have initially normal neutrophil findings (Absolute Neutrophil Count; ANC) ≥1500/mm^3(1.5x10^9/L) in general population and ≥1000/mm^3(1.0x10^9/L) in patients with confirmed benign ethnic neutropenia (BEN), and**
- **in whom regular absolute neutrophil counts (ANC) can be performed as follows: weekly during the first 18 weeks of therapy, then monthly for the following 34 weeks (i.e., until the completion of the first year of treatment). After 12 months, if there has been no history of neutropenia during the first year, ANC monitoring should be reduced to once every 12 weeks. After 24 months, an ANC count should be collected once a year, provided there has been no history of neutropenia during the previous two years. If mild neutropenia has occurred during treatment and has subsequently been stabilised and/or resolved, ANC monitoring should be performed monthly throughout treatment. ANC count must be performed immediately if signs or symptoms of infection occur (e.g. fever, sore throat, mouth/throat ulcers). Additional ANC count should be considered in older patients, and after addition of valproic acid to clozapine, especially during the initiation period. (see sections 4.4 and 4.5)Prescribing physicians should comply fully with the required safety measures. At each consultation, a patient receiving Denzapine must 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 (see section 4.4). Denzapine must be dispensed under strict medical supervision in accordance with official recommendations (see section 4.4).<u>Myocarditis</u>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 (see section 4.4). 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 (see section 4.4). If myocarditis or cardiomyopathy are suspected, Denzapine treatment should be promptly stopped and the patient immediately referred to a cardiologist (see section 4.4).Patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine (see section 4.3 and 4.4).

1 NAME OF THE MEDICINAL PRODUCT

Denzapine ®200 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

For Denzapine 200 mg Tablets: Each tablet contains 200 mg Clozapine.

Excipient(s) with known effect

One tablet contains 260 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

For Denzapine 200 mg Tablets: 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

Treatment-resistant schizophrenia
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.

Psychosis during the course of Parkinson's disease
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

Posology
The dosage must be adjusted individually. For each patient the lowest effective dose should be used. For doses not realisable/practicable with this strength, other strengths of this medicinal product are available. Cautious titration and a divided dosage schedule are necessary to minimise the risks of hypotension, seizure, and sedation.

Initiation of Denzapine treatment must be restricted to those patients with an absolute neutrophil count (ANC) ≥1500/mm^3 (1.5×10^9/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).

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.

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.

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 (see section 4.4).

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), but was then able to be successfully titrated to a therapeutic dose, re-titration should be carried out with extreme caution.

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

Starting therapy

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.

Therapeutic dose range

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.

Maximum dose

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.

Maintenance dose
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. In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

Special populations

Hepatic impairment
Patients with hepatic impairment should receive Denzapine with caution along with regular monitoring of liver function tests (see section 4.4).

Paediatric population
No paediatric studies have been performed. The safety and efficacy of Denzapine in children and adolescents under the age of 16 years have not yet been established. No data are available. It should not be used in this group until further data become available.

Patients 60 years of age and older
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.

Method of Administration
Oral

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- This product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase 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 clozapine-induced agranulocytosis.
- 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.
- 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.

4.4 Special warnings and precautions for use

Agranulocytosis

Denzapine can cause agranulocytosis. The incidence of agranulocytosis and the fatality rate in those developing agranulocytosis have decreased markedly since the institution of absolute neutrophil count (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 and:

- who have initially normal neutrophil findings (Absolute Neutrophil Count; ANC) ≥1500/mm^3(1.5x10^9/L) in general population and ≥1000/mm^3(1.0x10^9/L) in patients with confirmed benign ethnic neutropenia (BEN), and
- in whom regular ANC can be performed weekly for the first 18 weeks of therapy, and then monthly for the next 34 weeks.

After 12 months, if there has been no history of neutropenia during the first year, ANC should be monitored every 12 weeks. After 24 months, if there has been no history of neutropenia during the preceding two years, ANC must only be collected once a year. If mild neutropenia has occurred during treatment and has subsequently been stabilised and/or resolved, ANC monitoring should be performed monthly throughout treatment.

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.

Prescribing physicians must comply fully with the required safety measures.
Prior to treatment initiation, physicians must ensure, to the best of their knowledge, that the patient has not previously experienced an adverse haematological reaction to clozapine that necessitated its discontinuation. Prescriptions should not be issued for periods longer than the interval between two blood counts.
Immediate discontinuation of Denzapine is mandatory if the ANC is less than 1000/mm^3 (1.0 x 10^9 /L) at any time during Denzapine treatment. Patients in whom Denzapine has been discontinued as a result of ANC deficiencies must not be re-exposed to Denzapine.
At each consultation, a patient receiving Denzapine must 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. Patients and their caregivers must be informed that, in the event of any of these symptoms, they must have a blood cell count performed immediately. Prescribers are encouraged 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 with benign ethnic neutropenia (BEN) should be given special consideration and may be started on Denzapine with the agreement of a haematologist (see section "Patients with Benign Ethnic Neutropenia (BEN)").

<u>Absolute Neutrophil Count (ANC) Monitoring</u>
Differential blood counts must be performed within 10 days prior to initiating Denzapine treatment to ensure that only patients with ANC ≥1500/mm^3 (1.5 x 10^9/L)) will receive the drug. After the start of Denzapine treatment the ANC must be monitored weekly for the first 18 weeks, and then monthly for the next 34 weeks. After 12 months, if there has been no history of neutropenia during the first year, ANC should be monitored every 12 weeks. After 24 months, if there has been no history of neutropenia during the preceding two years, ANC must only be collected once a year. If mild neutropenia has occurred during treatment and has subsequently been stabilised and/or resolved, ANC monitoring should be performed monthly throughout treatment.
Monitoring must continue throughout treatment as reported before and for 4 weeks after complete discontinuation of Denzapine or until haematological recovery has occurred (see below Low ANC). At each consultation, the patient must be reminded to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. Differential blood counts must be performed immediately if any symptoms or signs of an infection occur.

<u>Low ANC</u>
If, during Denzapine therapy, the ANC falls to between 1500/mm^3 (1.5 x 10^9/L) and 1000/mm^3 (1.0 x 10^9/L), haematological evaluations must be performed at least twice weekly until the patient's ANC stabilises within the range 1000 - 1500/mm^3 (1.0 - 1.5 x 10^9/L), respectively, or higher. After stabilisation and/or resolution, ANC monitoring must be performed monthly throughout treatment.
Immediate discontinuation of Denzapine treatment is mandatory if the ANC is less than 1000/mm^3 (1.0 x 10^9/L) during Denzapine treatment. 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 1. Actions to be taken with Denzapine depending on ANC values for general population

Blood cell count	**Action required**
ANC/mm^3 (/L)	
≥1500 (≥1.5 x 10^9)	Continue Denzapine treatment
≥1000 to <1500 (≥1.0 x 10^9 to <1.5 x 10^9)	Continue Denzapine treatment, sample blood twice weekly until counts stabilise or increase and then monthly after stabilisation and/or resolution.
< 1000 (<1.0 x 10^9)	Immediately stop Denzapine treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

If Denzapinehas been withdrawn and the ANC falls below 1000/mm^3 (1.0 x 10^9/L), the management of this condition must be guided by an experienced haematologist.

Patients with Benign Ethnic Neutropenia (BEN)

In patients with confirmed BEN, the adjusted ANC threshold for starting or continuing clozapine is ANC ≥ 1000/mm^3 (1.0 × 10^9/ L). If the ANC is between 500 and 999/mm^3 (0.5–0.9×10^9/L), monitoring must be done twice weekly. Clozapine should be discontinued if the ANC falls below 500/mm^3 (0.5 × 10^9 /L).

Table 2. Actions to be taken with Denzapine depending on ANC values for BEN patients

ANC/mm^3 (/L)	**Action required**
≥1000 (≥1.0 x 10^9)	Continue Denzapine treatment
500 - 999 (0.5–0.9×10^9),	Continue Denzapine treatment, sample blood twice weekly until counts stabilise or increase and then monthly after stabilisation and/or resolution.
<500 (0.5 × 10^9).	Immediately stop Denzapine treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

Discontinuation of therapy for haematological reasons

Patients in whom Denzapine has been discontinued as a result of 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. Patients should be monitored weekly for 4 weeks in case of complete discontinuation.

Discontinuation of therapy for other reasons

Patients who have been on Denzapine for more than two years with no history of neutropenia and have had their treatment interrupted for causes different from neutropenia, do not need to resume the weekly monitoring schedule but the one used before the interruption, irrespective of the duration of interruption (i.e yearly controls). In case of complete discontinuation, those patients should not be monitored weekly for 4 weeks.

Patients who have been on Denzapine between 18 weeks and 2 years or for more than 2 years with history of mild neutropenia that did not lead to treatment interruption, or patients who have had their treatment interrupted for more than 3 days but less than 4 weeks should have their 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). In case of complete discontinuation those patients should be monitored weekly for 4 weeks.

Table 3 below summarises the ANC monitoring after Denzapine interruption.

Table 3. ANC monitoring upon resuming clozapine after treatment interruption for other reasons (not haematological)

Treatment duration before interruption	**Neutropenia episodes before interruption**	**Interruption duration**	**Recommended ANC monitoring**
≥ Two years	No	Irrelevant	Schedule used before the interruption (i.e yearly controls).
≥ Two years	Yes	3 days to <4 weeks	Weekly for 6 weeks. After that period, if no haematological abnormality occurs, monitor at intervals not exceeding 4 weeks.
> 18 weeks – Two years	Yes/No	3 days to <4 weeks	
≥ Two years	Yes	≥4 weeks	Weekly for the next 18 weeks of treatment, then monthly and dose should be re-titrated.
> 18 weeks – Two years	Yes/No	≥4 weeks	

Other precautions

Eosinophilia

In the event of **eosinophilia**, discontinuation of Denzapine is recommended if the eosinophil count rises above 3000/mm^3 (3.0 x 10^9/L); therapy should be restarted only after the eosinophil count has fallen below 1000/mm^3 (1.0 x 10^9/L).

Thrombocytopenia

In the event of **thrombocytopenia**, discontinuation of Denzapine therapy is recommended if the platelet count falls below 50 000/mm^3 (50 x 10^9/L).

Cardiovascular disorders

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 benzodiazepines or any other psychotropic agent (see section 4.5) 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 is suspected, Denzapine treatment should be promptly stopped and the patient immediately referred to a cardiologist.

In patients who are diagnosed with cardiomyopathy while on clozapine treatment, there is potential to develop mitral valve incompetence. Mitral valve incompetence has been reported in cases of cardiomyopathy related to clozapine treatment. These cases of mitral valve incompetence reported either mild or moderate mitral regurgitation on two-dimensional echocardiography (2DEcho) (see section 4.8).

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

Myocardial infarction

In addition, there have been post marketing reports of **myocardial infarction** which may be fatal. Causality assessment was difficult in the majority of these cases because of serious pre-existing cardiac disease and plausible alternative causes.

QT interval prolongation

As with other antipsychotics, caution should be exercised in patients with cardiovascular disease or a family history of **QT prolongation**.

As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase QTc interval.

Cerebrovascular Adverse Events

An approximately 3-fold increased risk of **cerebrovascular adverse events** has 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.

Risk of thromboembolism

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

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Denzapineand preventive measures undertaken.

Seizures

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) and, if necessary, an anti-convulsant treatment should be initiated.

Anticholinergic effects

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,paralytic ileus,appendicitis, megacolon** and **intestinal infarction ischaemia** (see section 4.8). 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.

Fever

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 ANC 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. If the diagnosis of NMS is confirmed, Denzapine must be discontinued immediately and appropriate medical measures should be administered.

Falls

Clozapine may cause seizures, somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions or medications that could exacerbate these effects, fall risk assessments must be completed when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Metabolic changes

Atypical antipsychotic drugs, including clozapine, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycaemia, dyslipidaemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific profile.

Hyperglycaemia

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. Patients with an established diagnosis of diabetes mellitis who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug. The discontinuation of clozapine should be considered in patients where active medical management of their hyperglycaemia has failed.

Dyslipidaemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including clozapine. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.

Weight gain

Weight gain has been observed with atypical antipsychotic use, including Denzapine. Clinical monitoring of weight is recommended.

Rebound, withdrawal effects

Acute withdrawal reactions have been reported following abrupt cessation of clozapine therefore gradual withdrawal 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.

Special populations

Hepatic impairment

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 Denzapine.

Patients aged 60 years and older

Initiation of treatment in the patients aged 60 years and older is recommended at a lower dose (see section 4.2).
Orthostatic hypotension can occur with Denzapine treatment and there have been reports of tachycardia, which may be sustained. Patients aged 60 years and older, particularly those with compromised cardiovascular function, may be more susceptible to these effects.
Patients aged 60 years and older may also be particularly susceptible to the anticholinergic effects of Denzapine, such as urinary retention and constipation.

Increased mortality in older people with dementia

Data from two large observational studies showed that older people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Denzapine is not approved for the treatment of dementia-related behavioural disturbances.

Severe cutaneous adverse reactions (SCARs)
Drug reaction with eosinophilia and systemic syndrome (DRESS), which can be life-threatening or fatal, have been reported in association with clozapine (see section 4.8).
Patients should be advised of the signs and symptoms of DRESS and monitored closely.
If signs and symptoms suggestive of this reaction appear, clozapine should be withdrawn immediately and an alternative treatment considered (as appropriate).
If the patient has developed DRESS with the use of clozapine, treatment with clozapine must not be restarted in this patient at any time.

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 must not be used concurrently with Denzapine (see section 4.3). These include co-trimoxazole, chloramphenicol, sulphonamides, pyrazolone analgesics e.g. phenylbutazone, penicillamine, carbamazepine or cytotoxic agents.
Long-acting depot antipsychotics (which have myelosuppressive potential) must 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).

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-alpha-adrenergic properties, Denzapine may reduce the blood-pressure-increasing effect of norepinephrine or other predominantly alpha-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), perazine, and the selective serotonin reuptake inhibitor fluvoxamine. 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. Hormonal contraceptives (including combinations of oestrogen and progesterone or progesterone only) are CYP 1A2, CYP 3A4 and CYP 2C19 inhibitors. Therefore, initiation or discontinuation of hormonal contraceptives may require dose adjustment of clozapine according to the individual medical need. 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 myelosuppresive

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).

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.

Concomitant treatment of clozapine and valproic acid may increase the risk of neutropenia and clozapine-induced myocarditis. If concomitant use of clozapine with valproic acid is necessary, careful monitoring is required.

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 I_C anti-arrhythmics, which are known to bind to cytochrome P450 2D6, no clinically relevant interactions have been observed thus far.

As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase the QT interval, because they may increase the risk of ventricular arrhythmias, including Torsades de Pointes. 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.

As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to cause electrolyte imbalance. Diuretics, in particular those causing hypokalaemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred.

An outline of drug interactions believed to be most important with Denzapine is given in Table 4 below (this is not an exhaustive list).

Table 4: Reference to the most common drug interactions with Denzapine

Drug	**Interactions**	**Comments**
Bone marrow suppressants (e.g. carbamazapine, chloramphenicol, sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics	Interact to increase the risk and/or severity of bone marrow suppression	Denzapine **must not be used** concomitantly with other agents having a well known potential to suppress bone marrow function (see Section 4.3)
Benzodiazepines	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.
Anticholinergics	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
Antihypertensives	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
Alcohol, MAOIs, CNS depressants, including narcotics and benzodiazepines	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
Highly protein bound drugs (e.g. warfarin and digoxin)	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
Phenytoin	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
Lithium	Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS)	Observe for signs and symptoms of NMS
CYP1A2 inducing substances (e.g. omeprazole)	Concomitant use may decrease clozapine levels	Potential for reduced efficacy of clozapine should be considered.
CYP1A2 inhibiting substances (e.g. fluvoxamine, caffeine, ciprofloxacin) , perazine, or hormonal contraceptives (CYP1A2, CYP3A4, CYP2C19)	Concomitant use may increase clozapine levels	Potential for increase in adverse effects. Care is also required upon cessation of concomitant CYP1A2 or CYP3A4 inhibiting medications as there will be a decrease in clozapine levels. The effect of CYP2C19 inhibition will be minimal.

4.6 Fertility, 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 section 5.3). Caution should be exercised when prescribing to pregnant women.

Neonates exposed to antipsychotics (including Denzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breast-feeding
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.

Fertility
Limited data available on the effects of clozapine on human fertility are inconclusive. In male and female rats, clozapine did not affect fertility when administered up to 40mg/kg, corresponding to a human equivalence dose of 6.4mg/kg, or approximately a third of the maximum permissible human dose.

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

Denzapine has a major influence on the 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

Summary of the safety profile
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). 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.

The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects and fever (see section 4.4). The most common side effects are drowsiness/sedation, dizziness, tachycardia, constipation, and hypersalivation.

Data from the clinical trials experience showed that a varying proportion of clozapine-treated patients (from 7.1 to 15.6%) were discontinued due to an adverse event, including only those that could be reasonably attributed to clozapine. The more common events considered to be causes of discontinuation were leucopenia, somnolence, dizziness (excluding vertigo) and psychotic disorder.

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 ANC count is mandatory (see section 4.4). Table 5 below summarises the estimated incidence of agranulocytosis for each Denzapine treatment period.

Table 5: Estimated incidence of agranulocytosis[1]

Treatment period	**Incidence of agranulocytosis per 100,000 person-weeks[2] of observation**
Weeks 0 - 18	32.0
Weeks 19 - 52	2.3
Weeks 53 and higher	1.8

[1] From the UK Patient Monitoring Service lifetime registry experience between 1989 and 2001.
[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 documented in patients with no known risk factors (see section 4.4).

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.

Very rare events of *ventricular tachycardia and* QT prolongation which may be associated with Torsades de Pointes have been observed although there is no conclusive causal relationship to the use of this medicine.

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.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs. The frequency is unknown.

Respiratory System
Respiratory depression or arrest has occurred very rarely, with or without circulatory collapse (see sections 4.4).

Gastrointestinal System
Constipation and hypersalivation have been observed very frequently, and nausea and vomiting frequently. Very rarely ileus may occur (see section 4.4). 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). 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.

Pregnancy, puerperium and perinatal conditions
Drug withdrawal syndrome neonatal (see section 4.6) has been reported. The frequency of this is not known.

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.

Acute withdrawal reactions have been reported (see section 4.4).

Tabulated list of adverse reactions
The table below (Table 6) summarises the adverse reactions accumulated from reports made spontaneously and during clinical studies.

Table 6: 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 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Infections and infestations	
Not known	Sepsis*
Blood and lymphatic system disorders	
Common	Leucopenia/decreased WBC/neutropenia, eosinophilia, leucocytosis
Uncommon	Agranulocytosis
Rare	Anaemia
Very rare	Thrombocytopenia, thrombocythaemia
Immune system disorders	
Not known	Angioedema*, leucocytoclastic vasculitis*, Drug rash with eosinophilia and systemic symptoms (DRESS)*
Endocrine disorders	
Not known	Pseudophaeochromocytoma *
Metabolism and nutrition disorders	
Common	Weight gain
Rare	Impaired glucose tolerance, diabetes mellitus, obesity*
Very rare	Ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypertriglyceridaemia, hypercholesterolaemia
Psychiatric disorders	
Common	Dysarthria
Uncommon	Dysphemia
Rare	Restlessness, agitation
Nervous system disorders	
Very common	Drowsiness/sedation,

	dizziness
Common	Blurred vision, headache, tremor, rigidity, akathisia, extra pyramidal symptoms, seizures/convulsions/myoclonic jerks
Uncommon	Neuroleptic malignant syndrome
Rare	Confusion, delirium
Very rare	Tardive dyskinesia, obsessive compulsive disorder
Not known	Cholinergic syndrome (after abrupt withdrawal)*, EEG changes*, pleurothotonus*, restless leg syndrome*
Cardiac disorders	
Very common	Tachycardia
Common	ECG changes
Rare	Circulatory collapse, Ventricular arrhythmias (VF, VT), myocarditis, pericarditis/pericardial effusion
Very rare	Cardiomyopathy, cardiac arrest,
Not known	Myocardial infarction *, myocarditits *, chest pain/angina pectoris*, atrial fibrillation*, palpitations*, mitral valve incompetence associated with clozapine related cardiomyopathy*
Vascular disorders	
Common	Hypertension, postural hypotension, syncope
Rare	Thromboembolism
Not known	Hypotension*, Venous thromboembolism
Respiratory, thoracic and mediastinal disorders	
Rare	Aspiration of ingested food, pneumonia and lower respiratory tract infection which may be fatal, sleep apnoea syndrome*
Very rare	Respiratory depression/arrest
Not known	Pleural effusion*, nasal congestion*
Gastrointestinal disorders	
Very common	Constipation, hypersalivation
Common	Nausea, vomiting, anorexia, dry mouth
Rare	Dysphagia
Very rare	Parotid gland enlargement, intestinal obstruction/paralytic ileus/faecal impaction
Not known	Megacolon*, intestinal

	infarction/ischaemia*, intestinal necrosis*, intestinal ulceration* and intestinal perforation* which may all be fatal Diarrhoea*, abdominal discomfort/heartburn/dyspepsia*, colitis*, appendicitis *, **, ***
Hepatobiliary disorders	
Common	Elevated liver enzymes
Rare	Hepatitis, cholestatic jaundice, pancreatitis
Very rare	Fulminant hepatic necrosis
Not known	Hepatic steatosis*, hepatic necrosis*, hepatotoxicity*, hepatic fibrosis*, hepatic cirrhosis*, liver disorders including those hepatic events leading to life-threatening consequences such as liver injury (hepatic, cholestatic and mixed), liver failure which may be fatal and liver transplant*.
Skin and subcutaneous tissue disorders	
Very rare	Skin reactions
Not known	Pigmentation disorder*
Musculoskeletal and connective tissue disorders	
Not known	Rhabdomyolysis*, muscle weakness*, muscle spasms*, muscle pain*, systemic lupus erythematous*
Renal and urinary disorders	
Common	Urinary incontinence, urinary retention
Very rare	Interstitial nephritis
Not known	Renal failure*, Nocturnal enuresis*
Pregnancy, puerperium and perinatal conditions	
Not known	Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders	
Very rare	Priapism
Not known	Retrograde ejaculation*
General disorders and administration site conditions	
Common	Fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation
Very rare	Sudden unexplained death
Not known:	Polyserositis*
Investigations	
Rare	Increased CPK
Injury, poisoning and procedural complications	
Uncommon	Falls (associated with clozapine-induced seizures,

	somnolence, postural hypotension, motor and sensory instability)*
System Organ Class: Neoplasms Benign, malignant and unspecified (incl cysts and polyps)	
Not known	Haematological malignancy

* Adverse drug reactions derived from post-marketing experience via spontaneous case reports and literature cases for the drug substance, Clozapine.

Reporting of suspected adverse reactions
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Website: www.hpra.ie. By reporting side affects you can help provide more information on the safety of this medicine.

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
There are no specific antidotes for Denzapine.

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: Antipsychotics; diazepines, oxazepines and thiazepines (ATC code N05A H02)

Mechanism of action
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 D_1, D_2, D_3 and D_5 receptors, but shows high potency for the D_4 receptor.

Pharmacodynamic effects
Clozapine has potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal-reaction-inhibiting effects. It has also been shown to possess antiserotoninergic properties.

Clinical efficacy and safety
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) and in whom regular haematological examinations can be performed (see sections 4.4 and 4.8).

5.2 Pharmacokinetic properties

Absorption
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%.

Distribution
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.

Biotransformation/metabolism
Clozapine is almost completely metabolised before excretion by CYP1A2 and CYP3A4, and to some extent by CYP2C19 and CYP2D6. Of the main metabolites only the desmethyl metabolite was found to be active. Its pharmacological actions resemble those of clozapine, but are considerably weaker and of short duration.

Elimination
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. 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.

Linearity/non-linearity
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.

5.3 Preclinical safety data

Non-clinical 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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Micro-Crystalline Cellulose
Lactose monohydrate
Povidone
Sodium Starch Glycolate A
Magnesium Stearate

6.2 Incompatibilities

Not applicable

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/ Aluminium Foil Blister Strips in a cardboard carton containing 20 or 50 tablets.
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 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
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E91 D768
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8 MARKETING AUTHORISATION NUMBER

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