Package leaflet: Information for the user

DENZAPINE® 25, 50, 100, 200 mg Tablets

Clozapine

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 because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Denzapine is and what it is used for
2. What you need to know before you take Denzapine
3. How to take Denzapine
4. Possible side effects
5. How to store Denzapine
6. Contents of the pack and other information

1. What Denzapine is and what it is used for

Denzapine contains the active substance 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, feels and behaves.

Denzapine is used:

- to treat schizophrenia when at least two other antipsychotic medicines, including one of the newer atypical antipsychotics, 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. What you need to know before you take Denzapine

Do not take Denzapine:

- if you are allergic to clozapine or to any of the other ingredients of this medicine (listed in section 6). 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
  - total lactase deficiency
  - glucose-galactose malabsorption
- if you are unable to undergo regular blood tests
- if you have a low number of white cells in the blood (leucopenia/granulocytopenia/agranulocytosis) especially if this was caused by medicines including previous treatment with clozapine. This does not apply if you have had low white blood cell count caused by previous chemotherapy.
- if you are receiving treatment with other medicines that can cause a fall in the number of white blood cells
- if you are being treated or have been treated with long-acting depot injections of antipsychotics
- If you use any medicine that stops your bone marrow from working properly
- if you have any of the following diseases:
  - Disorders of the bone marrow (when the bone marrow does not make enough blood cells) or have ever suffered from bone marrow disease
  - Uncontrolled epilepsy (fits or seizures)
  - Acute mental illness caused by alcohol, medicines or other substances (e.g. narcotics)
  - Circulatory collapse (a very pronounced fall in the blood pressure that may lead to unconsciousness)
  - Disorders affecting the brain that can lead to severe drowsiness, reduced consciousness or unconsciousness
  - Severe kidney disease
  - Heart disease (such as myocarditis (inflammation of heart muscle), pericarditis (inflammation of the pericardium) or cardiomyopathy (weakness of heart muscle))
  - Active liver disease with jaundice (yellow colouration of the skin and eyes), feeling sick and loss of appetite
  - Liver failure or any other severe liver disease
  - Paralytic ileus (a disorder of the small intestine)

<u>Denzapine must not be given to anyone who is unconscious or in a coma.</u>

Warnings and precautions

The safety measures mentioned in this section are very important. You must comply with them to minimise the risk of serious life-threatening side effects.

Talk to your doctor or pharmacist before taking Denzapine if you have or have had any medical conditions or illnesses, especially the following:

- Low number of white blood cells (leucopenia, 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 have had a heart disease or family history of abnormal conduction in the heart called "prolongation of the QT interval"
- Orthostatic hypotension (a fall in the blood pressure on standing up)
- Epilepsy or fits, even if they are well controlled
- Any heart, kidney, or liver disease
- Enlargement of the prostate or difficulty urinating
- Glaucoma (raised pressure in the eye)
- Severe or chronic constipation or if you are taking medicines which cause constipation (such as anticholinergics)
- Paralytic ileus, disease of the large bowel
- operations on the abdomen
- Diabetes. Increased blood sugar levels have occurred in patients with or without diabetes mellitus in their medical history (see section 4).
- Stroke (risk factors of stroke e.g. smoking, diabetes and high blood pressure)
- If you or someone else in your family has a history of blood clots, as medicines like these have been associated with formation of blood clots. If you are not mobile you are at increased risk of developing blood clots while taking Denzapine

Talk to your doctor or pharmacist **immediately**

- if you have **constipation, abdominal pain, abdominal tenderness, fever, bloating** and/or **bloody diarrhoea**. Your doctor will have to treat this in order to avoid further complications
- if you experience symptoms such as a **sudden increase in body temperature, sweating, a fast heart beat, muscle stiffness and a fluctuating blood pressure**, this may be caused by Neuroleptic Malignant Syndrome - a serious reaction to some anti-psychotic medicines. It can lead to coma. Stop taking Denzapine immediately if your doctor or pharmacist tells you
- if you get signs of a **cold, fever, flu-like symptoms, sore throat or any other infection**. You will have to have an urgent blood test to check if your symptoms are related to your medicine
- if you have **fast and irregular heartbeat**, even when you are at rest, **palpitations, breathing problems, chest pain** or **unexplained tiredness**. Your doctor will need to check your heart and if necessary refer you to a cardiologist immediately
- if you experience **nausea (feeling sick), vomiting (being sick)** and/or **loss of appetite**. Your doctor will need to check your liver

Medical check-ups and blood tests

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.

Your doctor will tell you exactly when and where to have the tests. Denzapine may only be taken if you have a normal blood count.

Denzapine can cause agranulocytosis. In this condition, the number of white blood cells (which are necessary to fight 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 must 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 18 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.

You will need to have blood tests for another 4 weeks after the end of Denzapine treatment. Your doctor will also do a physical examination before starting treatment. Your doctor may do an electrocardiogram (ECG) to check your heart, but only if this is necessary for you, or if you have any special concerns.

Denzapine may cause alteration in blood lipids (fats), and may cause weight gain. Your doctor may monitor your weight and blood lipid level.

If you have a liver disorder you will need regular liver function tests for as long as you continue to take Denzapine.

If Denzapine makes you feel light-headed, dizzy or faint, or if you already suffer from these feelings, be careful when getting up from a sitting or lying position as this may increase the possibility of falling.

If you have to undergo surgery or if for some reason you are unable to walk around for a long time, discuss with your doctor the fact that you are taking Denzapine. You may be at risk of thrombosis (blood clotting within a vein).

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.

Children and adolescents under 16 years

Do not use Denzapine if you are under 16 years of age because there is not enough information about its use in this age group.

Older people (aged 60 years and over)

Some side effects are more common in older people: feeling dizzy or faint when you stand up or change position, fast heart beat, difficulty passing urine, and constipation.

Tell your doctor or pharmacist if you suffer from Dementia.

Other medicines and Denzapine

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. This includes medicines obtained without a prescription or herbal therapies. You might need to take different amounts of your medicines or to take different medicines.

Do not take Denzapine together with medicines that stop the bone marrow from working properly and/or decrease the number of blood cells produced by the body, such as:

- 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)

Taking Denzapine at the same time as another medicine may affect how well Denzapine and/or the other medicine works. Tell your doctor if you plan to take, if you are taking (even if the course of treatment is about to end) or if you have recently had to stop taking any of the following medicines:

- Medicines that can make you drowsy e.g. morphine (for pain), benzodiazepines (for anxiety or as sleeping pills) and antihistamines (for allergies or colds) such as loratadine, chlorpheniramine
- Other antipsychotic medicines used to treat mental illnesses such as perazine
- Anticholinergic medicines, which are used to relieve stomach cramps, spasms and travel sickness
- Medicines used to treat high blood pressure, e.g. metoprolol, captopril, enalapril
- 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 miconazole
- Medicines to treat epilepsy e.g. phenytoin, carbamazepine, valproic acid
- Medicines for depression, such as fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram, amitriptyline, phenelzine, moclobemide, chlorpromazine, mesoridazine or fluphenazine
- Lithium (for mental disorders)
- Medicines which affect how your body eliminates clozapine. Your doctor will know which medicines these are.
- Omeprazole (a drug used to treat excess stomach acid)
- Ciprofloxacin (a drug used to treat infections)
- Hormonal contraceptives (birth control tablets)
- Medicines used to treat viral infections such as protease inhibitors used to treat HIV infection
- Narcotics and other medicines which can affect your breathing

This list is not complete. Your doctor and pharmacist have more information on medicines to be careful with or to avoid while taking Denzapine. They will also know if the medicines you are taking belong to the listed groups. Speak to them.

Denzapine with food, drink, and alcohol

You can take your Denzapine tablets with or without food.

Do not drink alcohol during treatment with Denzapine.

Caffeine can affect the levels of clozapine (the active substance of Denzapine) in your blood. You may drink coffee, tea, cola and other drinks containing caffeine. However, if you stop drinking caffeine suddenly, the levels of clozapine in your blood may fall. This will make the medicine less effective. Equally, if you start drinking caffeine, the levels may rise, increasing the risk of side effects.

Smoking

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

Pregnancy

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. 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. Tell your doctor immediately if you become pregnant during treatment with Denzapine.

The following symptoms may occur in newborn babies, of mothers that have used Denzapine in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms contact your doctor.

Breast-feeding

Do not breast-feed when using Denzapine because the active ingredient, clozapine, can reach your baby through your breast milk.

Fertility

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.

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.

Denzapine contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Denzapine

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

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. It is important that you do not change your dose or stop taking Denzapine without asking your doctor first.

Do not use Denzapine to treat other complaints unless your doctor tells you to.

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.

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

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 low or too high, talk to your doctor.

Recommended dose

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 bed time. 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.

Patients with schizophrenia that is resistant to other treatments

The usual starting dose is 12.5 mg (one half of a 25 mg tablet) once or twice on the first day followed by 25 mg once or twice on the second day. Swallow the tablet with water. If tolerated well, your doctor will then gradually increase the dose in steps of 25-50 mg over the next 2-3 weeks until a dose up to 300 mg per day is reached. Thereafter, if necessary, the daily dose may be increased in steps of 50 to 100 mg half-weekly or, preferably, at weekly intervals.

Continued over the page

The effective daily dose is usually between 200 mg and 450 mg, divided into several single doses per day. Some people might need more. A daily dose of up to 900 mg is allowed. Increased side effects (in particular seizures) are possible at daily doses over 450 mg. Always take the lowest effective dose for you. Most people take part of their dose in the morning and part in the evening. Your doctor will tell you exactly how to divide your daily dose. If your daily dose is only 200 mg, then you can take this as a single dose in the evening. Once you have been taking Denzapine with successful results for some time, your doctor may try you on a lower dose. You will need to take Denzapine for at least 6 months.

Treatment of severe thought disturbances in patients with Parkinson's disease
The usual starting dose is 12.5 mg (one half of a 25 mg tablet) in the evening. Swallow the tablet with water. Your doctor will then gradually increase the dose in steps of 12.5 mg, not faster than two steps a week, up to a maximum dose of 50 mg by the end of the second week. Increases in the dosage should be stopped or postponed if you feel faint, light-headed or confused. In order to avoid such symptoms your blood pressure will be measured during the first weeks of treatment.

The effective daily dose is usually between 25 mg and 37.5 mg, taken as one dose in the evening. Doses of 50 mg per day should only be exceeded in exceptional cases. The maximum daily dose is 100 mg. Always take the lowest effective dose for you.

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.

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.

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, tiredness
– incoherent speech
– confusion and coma
– delirium
– agitation
– lack of energy
– light-headedness
– hallucinations
– a fall in the blood pressure
– collapse
– widening of the black part of the eye, blurred vision
– shallow or slow breathing or sometimes shortness of breath
– fast or irregular heart beat
– dribbling
– fits
– trembling hands
– unconsciousness
– stiff limbs

If you forget to take Denzapine
If it is almost time for your next dose (within four hours), leave out 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 a 48 hour period, 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 you stop taking Denzapine
Do not stop taking Denzapine or lower the dosage even if you are feeling better, unless your doctor tells you to do so because you might get withdrawal reactions. These reactions include sweating, headache, nausea (feeling sick), vomiting (being sick) and diarrhoea. **If you have any of the above signs, tell your doctor straight away. These signs may be followed by more serious side effects unless you are treated immediately.** 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**.**

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 psychotic symptoms. Other symptoms can also arise, including increased sweating, headache, nausea (feeling sick), vomiting and diarrhoea.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects below can be serious and need immediate medical attention:

Tell your doctor immediately before taking the next Denzapine tablet if you experience any of the following:

Very common (may affect more than 1 in 10 people):
- severe constipation. Your doctor will have to treat this in order to avoid further complications
- a fast heart beat (tachycardia)

Common (may affect up to 1 in 10 people):
- a fall in the number of white cells in the blood (leucopenia, neutropenia, granulocytopenia) (see Section 3, "How to take Denzapine")
- an increase in the number of a certain type of white blood cells called eosinophil granulocytes (eosinophilia)
- an increase in the number of white blood cells (leukocytosis). Your blood must be monitored to detect these conditions.
- signs of a cold, fever, flu-like symptoms, sore throat or any other infection, tell your doctor immediately
- changes on the heart trace (ECG)
- seizures, convulsions or sudden, brief involuntary twitching or jerking
- a fall in the blood pressure on standing up (orthostatic hypotension)
- fainting

Uncommon (may affect up to 1 in 100 people):
- a very low number of white cells in the blood (agranulocytosis)
- a sudden rapid increase in body temperature, rigid muscles which may lead to unconsciousness (neuroleptic malignant syndrome) as you may be experiencing a serious side effect which requires immediate treatment
- light-headedness, dizziness or fainting, when getting up from a sitting or lying position as it may increase the possibility of falling

Rare (may affect up to 1 in 1,000 people):
- impaired glucose tolerance (excess sugar levels in the blood)
- diabetes mellitus, or worsening of existing diabetes
- 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)
- inflammation of the membranes around the heart (pericarditis)
- a collection of liquid in the membranes around the heart (pericardial effusion)
- blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately.
- yellow colouration of the skin and eyes (jaundice). If you notice these symptoms stop taking Denzapine immediately and seek medical advice.
- nausea (feeling sick), vomiting (being sick) and/or loss of appetite. Your doctor will need to check your liver.
- inflammation of the liver (hepatitis)
- inflammation of the pancreas (pancreatitis)
- signs of a respiratory tract infection or pneumonia such as fever, coughing, difficulty breathing, wheezing
- interruption in breathing with or without snoring during sleep
- signs of becoming obese or increasing obesity

Very rare (may affect up to 1 in 10,000 people):
- slow, abnormal movements of the face, tongue and limbs (tardive dyskinesia)
- cardiac arrest
- disease of the heart muscle (cardiomyopathy)
- abnormality of electrocardiogram (ECG) called QT prolongation
- Torsades de pointes (a life-threatening disorder of the heart. This is a medical emergency)
- sudden unexplained death
- very slow or shallow breathing (respiratory depression)
- absence of breathing (respiratory arrest)
- altered bowel movement (intestinal obstruction, paralysis of the small intestine, faecal impaction)
- death of the liver (fulminant hepatic necrosis)
- inflammation of the kidney (interstitial nephritis)
- in elderly people with dementia, a small increase in the number of people dying has been reported for patients taking antipsychotics compared with those not taking antipsychotics
- a persistent and possibly painful erection (priapism). If you have an erection which lasts more than 4 hours immediate medical treatment may be needed in order to avoid further complications.
- a change in the number of platelets in the blood outside the normal range (thrombocytopenia, thrombocythaemia)
- complications of excessive sugar in the blood (severe hyperglycaemia, ketoacidosis, hyperosmolar coma)

Not known (frequency cannot be estimated from the available data):
- changes in normal patterns of brain activity detected (EEG)
- heart attack
- chest pain, including pain which spreads to the arms and shoulders
- intermittent "thumping", "pounding"or "fluttering" sensation in the chest (palpitations)
- rapid and irregular heartbeats (atrial fibrillation). There may be occasional heart palpitations, fainting, shortness of breath, or chest discomfort
- symptoms of low blood pressure (hypotension) such as light-headedness, dizziness, fainting, blurred vision, unusual fatigue, cold and clammy skin or nausea
- shortness of breath, fatigue, palpitations, swollen feet and ankles due to a heart disorder where the mitral valve does not close properly when the heart pumps out blood (mitral valve incompetence). This would be detected via a heart scan
- blood clots in the veins
- proven or strongly suspected infection along with fever or low body temperature, abnormally rapid breathing, rapid heart rate, change in responsiveness and awareness, drop in blood pressure (sepsis)
- death of parts of the liver
- damage to the liver caused by chemicals
- failure of the liver to heal correctly (hepatic fibrosis, hepatic cirrhosis)
- other liver disorders which may result in death or require liver transplant
- kidney failure
- allergic reaction (swelling mainly of the face, mouth and throat, as well as the tongue, which may be itchy or painful)
- profuse sweating, headache, nausea, vomiting and diarrhoea (symptoms of cholinergic syndrome)
- loss of appetite, swollen abdomen, abdominal pain, yellowing of the skin, severe weakness and malaise. This may indicate possible liver disorders that involve replacement of normal liver tissue with scar tissue leading to loss of liver function, including those liver events leading to life threatening consequences such as liver failure (which may lead to death), liver injury (injury of the liver cells, bile duct in the liver, or both) and liver transplant
- burning upper abdominal pain, particularly between meals, early in the morning, or after drinking acidic drinks; tarry, black, or bloody stools; bloating, heartburn, nausea or vomiting, early feeling of fullness (intestinal ulceration of stomach and/or gut) which may lead to death
- severe abdominal pain intensified by movement, nausea, vomiting including vomiting blood (or liquid with what looks like coffee grounds); abdomen becomes rigid with (rebound) tenderness spreading from point of perforation across the abdomen; fever and/or chills (intestinal perforation of stomach and/or gut or ruptured bowel) which may lead to death
- constipation, abdominal pain, abdominal tenderness, fever, bloating, bloody diarrhoea. This may indicate possible megacolon (enlargement of the intestines) or intestinal infarction/ischaemia. Your doctor will need to examine you
- increased or new muscle weakness, muscle spasms, muscle pain. This may indicate a muscle disorder (rhabdomyolysis). Your doctor will need to examine you
- sharp chest or abdominal pain with shortness of breath, with or without coughing or fever
- extremely intense and serious skin reactions, such as drug rash with eosinophilia and systemic symptoms (DRESS syndrome), have been reported during use of Denzapine. The adverse reaction of the skin may appear as rashes with or without blisters. Skin irritation, oedema and fever and flu-like symptoms may occur. Symptoms of DRESS syndrome usually appear approximately 2-6 weeks (possibly up to 8 weeks) after treatment begins
- Pleural effusion – build-up of fluid in the lining of the lungs
- inflammation of the colon (colitis)
- inflammation of membranes which line the chest, abdomen and joints (Polyserositis)

The following side effects have also been associated with Denzapine:

Very common (may affect more than 1 in 10 people):
hypersalivation (forming a large volume of saliva), drowsiness, dizziness.

Common (may affect up to 1 in 10 people):
fatigue, weight gain, blurred vision, headache, tremor, stiffness of the limbs (rigidity), restlessness (akathisia), problems of coordination, high blood pressure (hypertension), 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), tiredness, fever, benign hyperthermia (drug fever; changes in body temperature caused by certain medicines), alterations in the body's control of temperature, alterations of sweating, slurring of words, abnormal movements, inability to initiate movement, inability to remain motionless, sudden loss of consciousness.

Uncommon (may affect up to 1 in 100 people):
speech disorders (e.g. stuttering).

Rare (may affect up to 1 in 1,000 people):
agitation, confusion, delirium, inhaling of food into the lungs (aspiration), difficulty swallowing (dysphagia), a rise in the CPK values (detected via a blood test), a low number of red blood cells (anaemia), serious chest infection.

Very rare (may affect up to 1 in 10,000 people):
excessive fat in the blood (hypertriglyceridaemia, hypercholesterolaemia), enlargement of the parotid glands (salivary glands), skin reactions, obsessive thoughts and compulsive behaviours (obsessive compulsive symptoms).

Not known (frequency cannot be estimated from the available data):
blocked nose, diarrhoea, stomach discomfort, heartburn, indigestion, accumulation of fat in the liver, muscle weakness or spasms or pain, bedwetting while asleep, sudden uncontrollable increase in blood pressure (pseudophaeochromocytoma), uncontrolled bending of the body to one side (pleurothotonus), ejaculatory disorder, rash, purplish-red spots, fever or itching due to inflammation of blood vessel, change in skin colour, "butterfly" facial rash, joint pain, muscle pain, fever and fatigue lupus erythematous, restless legs syndrome (irresistible urge to move your legs or arms, usually accompanied by uncomfortable sensations during periods of rest, especially in the evening or at night and temporarily relieved by movement).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via MHRA Yellow Card Scheme: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Denzapine

Keep this medicine out of the sight and reach of children.

A locked cupboard at least one and a half metres from the ground is a good place to store medicines.

Do not use this medicine after the expiry date which is stated 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.

Store Denzapine at a temperature at or below 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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other 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 mg 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 50 or 100 tablets and in blister packs containing 20, 50 or 100 tablets.
Denzapine 200 mg tablets are supplied in bottles of 50 or 100 tablets and in blister packs containing 20 or 50 tablets.

Not all pack sizes may be marketed.

The quantity provided to you by the pharmacy will be determined by your doctor.

The Marketing Authorisation holder and manufacturer:
Britannia Pharmaceuticals Ltd.
200 Longwater Avenue, Green Park, Reading, Berkshire RG2 6GP, 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 04483/0067
Denzapine 50 mg tablets PL 04483/0068
Denzapine 100 mg tablets PL 04483/0069
Denzapine 200 mg tablets PL 04483/0070

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BRITANNIA PHARMACEUTICALS LTD

Product Title	Denzapine Tablet	**Date**	02/05/2023
Manufacturer		**Client**	Britannia
Item	Leaflet	**Country**	GB & NI
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_04	17/10/2023	Major text amendments
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_06	05/12/2023	Minor text amendments
_07	05/06/2025	Minor text amendments