DENZAPINE® clozapine

RED PROTOCOL

Denzapine Monitoring Service:
Tel – 0333 200 4141
Fax – 0333 200 4142

Britannia Switchboard:
Tel – 01189 209 559

DENZAPINE PATIENT

RED RESULT GENERATED*
WBC < 3.0 and/or ANC < 1.5 and/or PLATELETS < 50 (x 10^9/L)

HCP & PATIENT RED PROTOCOL

1. Collection centre need to bring in patient for DAILY blood testing in order to confirm RED result not spurious. Analyse
2. Dispensing NOT permitted. Excess medication should be retrieved to ensure patient ceases therapy.
3. Consultant should be made aware of the situation immediately.
4. Under NO circumstances should the patient be restarted on Denzapine, until the 'RECHALLENGE' procedure' has been completed.

Contact the DMS team to initiate a re-challenge.

It is vital that the primary contacts for every patient are kept updated – in case of adverse events.

DMS TEAM RED PROTOCOL

1. Collection centre are made aware of the RED result via phone.
2. Pharmacy is made aware via phone and fax.
3. RED letter faxed and posted to the patients consultant.
4. Britannia Haematologist made aware of RED patient.
5. If the RED result is considered 'SPURIOUS' by Britannia Haematologist. DMS team will remove RED result and patient will resume normal monitoring unless there has been a break in treatment of > 48 hours.

*BEN & 'Special Monitoring' patients are treated on a patient by patient basis.

BRITANNIA PHARMACEUTICALS LTD

DENZAPINE ABBREVIATED PRESCRIBING INFORMATION

DENZAPINE includes the active ingredient clozapine at doses of either 25 mg or 100mg tablets or a 50mg/ml Suspension

Indications Treatment-resistant schizophrenic patients. Schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics. Psychotic disorders occurring during Parkinson's disease, in cases where standard treatment has failed. **Dosage and Administration** Clozapine dosing must be individualised by cautious titration. Start with 12.5 mg once or twice daily on the first day, followed by one or two 25 mg tablets on the second day. The daily dose may then be increased by 25 to 50 mg in order to achieve a dose level of 300 mg/day within 2-3 weeks. The daily dose may then be increased by 50 to 100 mg at half-weekly, or weekly intervals. Maximum doses up to 900 mg daily may be used. An increased risk of adverse reactions (in particular seizures) occurs at higher doses, in particular doses over 450 mg/day. For special patient populations refer to the full prescribing information for a more gradual titration. **Contraindications** Hypersensitivity to DENZAPINE or any excipients. Galactose intolerance, Lapp lactose intolerance deficiency or glucose-galactose malabsorption, patients unable to undergo regular blood tests. History of toxic or idiosyncratic granulocytopenia/agranulocytosis (unless from prior chemotherapy). Prior DENZAPINE-induced agranulocytosis. Bone marrow impairment. Uncontrolled epilepsy. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions. Circulatory collapse and/or CNS depression, severe renal or cardiac disorders (e.g. myocarditis). Active or progressive liver disease. Hepatic failure. Paralytic ileus. Concurrent treatment with drugs that have substantial potential for causing agranulocytosis. Concurrent use of depot antipsychotics is discouraged. Prior clozapine-induced myocarditis or cardiomyopathy patients, should not be re-exposed to clozapine. **Warnings and Precautions** DENZAPINE can cause agranulocytosis. It can only be prescribed to patients who have initially normal leukocyte findings (white blood cell count of >3500/mm^3 (3.5 x 10^9/l), and an absolute neutrophil count (ANC) of >2000/mm^3 (2.0 x 10^9/l)), in whom regular white blood cell (WBC) counts and absolute neutrophil counts (ANC) can be performed throughout treatment and for 4 weeks after complete discontinuation. DENZAPINE is associated with an increased risk of myocarditis, which in rare cases have been fatal. Fatal cases of cardiomyopathy have also been reported rarely. Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, and/or palpitations, arrhythmias, chest pain and other signs or symptoms of heart failure, or symptoms that mimic myocardial infarction. Patients with a 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. The treating physician should consider performing a pre-treatment ECG. If myocarditis or cardiomyopathy is suspected treatment should be ceased and a cardiologist consulted. Patients must be under specialist supervision. DENZAPINE supply is restricted to physicians patients and pharmacies registered with the Denzapine Monitoring Service (DMS). This service provides for the required leucocyte counts and a drug supply audit so that DENZAPINE is promptly withdrawn from any patient who develops abnormal leucocyte findings. Patients should be reminded to contact their physician immediately if any kind of infection begins to develop, especially if flu-like. Immediate differential count is necessary if signs of infection develop. Re-evaluate any patient developing an infection, or when a routine WBC count is between 3.0 and 3.5 x 10^9/l and/or an ANC between 1.5 and 2.0 x 10^9/l. Haematological evaluations must be performed twice weekly until the patient's WBC and ANC stabilise at values above 3.5 x 10^9/l and 2.0 x 10^9/l respectively. If the WBC count falls below 3.0 x 10^9/l and/or the ANC drops below 1.5 x 10^9/l, withdraw DENZAPINE immediately, sample blood daily and monitor the patient closely, for signs of infection. Orthostatic hypotension can occur, therefore close medical supervision is required during initial dose titration, particularly in the elderly. DENZAPINE can cause sedation and lower the seizure threshold. Activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment. Monitor hepatic function regularly in patients with stable pre-existing liver disorders. Carry out LFTs in patients that develop symptoms of possible liver dysfunction during DENZAPINE therapy. If the elevation of the values is clinically relevant or if symptoms of jaundice occur, treatment with DENZAPINE must be discontinued and may be resumed only when the results of liver function tests are normal. DENZAPINE can cause unwanted effects through anticholinergic activity, therefore use with care in patients with prostatic enlargement and narrow-angle glaucoma. DENZAPINE has been associated with varying degrees of intestinal peristalsis impairment, cases of which have been fatal. Patients with fever should be carefully evaluated to rule out an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome must be considered. Avoid immobilisation of patients due to increased risk of thromboembolism. Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely. The discontinuation of DENZAPINE should be considered in patients where active medical management of their hyperglycaemia has failed. Do not use in pregnant or lactating women. Use adequate contraceptive measures in women of child bearing potential. The concomitant administration of neuroleptic medicines should be avoided. DENZAPINE should be used with caution in patients with risk factors for stroke. Prescriptions should not be issued for periods longer than the interval between two blood counts. Immediate discontinuation of DENZAPINE is mandatory if either the WBC count is less than 3000/mm^3 (3.0 x 10^9/l) or the ANC is less than 1500/mm^3 (1.5 x 10^9/l) at any time during DENZAPINE treatment. Patients in whom DENZAPINE has been discontinued as a result of either WBC or ANC deficiencies must not be re-exposed to DENZAPINE. At each consultation, a patient should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia or agranulocytosis. Patients with a history of primary bone marrow disorders may be treated only if the benefit outweighs the risk. They should be carefully reviewed by a haematologist prior to starting DENZAPINE. Patients who have low WBC counts because of benign ethnic neutropenia should be given special consideration and may be started on DENZAPINE with the agreement of a haematologist. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of DENZAPINE or until haematological recovery has occurred (see below Low WBC count/ANC). If, during DENZAPINE therapy, either the WBC count falls to between 3500/mm^3 (3.5 x 10^9/l) and 3000/mm^3 (3.0 x 10^9/l) or the ANC falls to between 2000/mm^3 (2.0 x 10^9/l) and 1500/mm^3 (1.5 x 10^9/l), haematological evaluations must be performed at least twice weekly until the patient's WBC count and ANC stabilise within the range 3000-3500/mm^3 (3.0 - 3.5 x 10^9/l) and 1500-2000/mm^3 (1.5 - 2.0 x 10^9/l), respectively, or higher. Immediate discontinuation of DENZAPINE treatment is mandatory if either the WBC count is less than 3000/mm^3 (3.0 x 10^9/l) or the ANC is less than 1500/mm^3 (1.5 x 10^9/l) during DENZAPINE treatment. WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Confirmation of the haematological values is recommended by performing two blood counts on two consecutive days; however, DENZAPINE should be discontinued after the first blood count. Following discontinuation of DENZAPINE, haematological evaluation is required until haematological recovery has occurred. 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). Discontinuation of DENZAPINE therapy is recommended if the platelet count falls below 50 000/mm^3 (50 x 10^9/l). Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease. If myocarditis or cardiomyopathy are suspected, DENZAPINE treatment should be promptly stopped and the patient immediately referred to a cardiologist. Patients with a history of epilepsy should be closely observed during therapy. Monitor for symptoms of DENZAPINE anticholinergic activity. DENZAPINE may be associated with thromboembolism, immobilisation of patients should be avoided. Initiation of treatment in the elderly is recommended at a lower dose. Monitor elderly patients, particularly those with compromised cardiovascular function, who may be more susceptible to orthostatic hypotension. Elderly patients may also be particularly susceptible to the anticholinergic effects. **Interactions** Drugs known to have a substantial potential to depress bone marrow function should not be used concurrently including: co-trimoxazole, chloramphenicol, sulphonamides, pyrazolone analgesics e.g. phenylbutazone, penicillamine, carbamazepine or cytotoxic agents. Long-acting depot antipsychotics (which have myelosuppressive potential) and alcohol should not be used concomitantly. CNS depressants such as narcotics, antihistamines, and benzodiazepines. Drugs possessing anticholinergic, hypotensive, or respiratory depressant effects may have an additive effect. Drugs known to inhibit cytochrome P450 isozymes may increase the levels of clozapine, Specifically CYP 1A2 inhibitors such as caffeine and SSRIs fluvoxamine, paroxetine, fluoxetine, and to a lesser degree sertraline - CYP 2D6 inhibitors. Pharmacokinetic interactions with CYP 3A4 inhibitors such as azole antimycotics, cimetidine, erythromycin, and protease inhibitors are unlikely, although some have been reported. Caffeine intake can increase clozapine plasma concentration. Sudden cessation of smoking may increase the plasma clozapine concentration. Citalopram interactions have been reported. Inducers of cytochrome P450 enzymes may decrease the plasma levels of clozapine. Inducers of CYP 450 enzymes include carbamazepine (not to be used concomitantly with clozapine, due to its myelosuppresive potential), phenytoin and rifampicin. Known inducers of CYP 1A2 such as omeprazole, may lead to decreased clozapine levels. Lithium or other CNS-active agents may increase the risk of development of neuroleptic malignant syndrome (NMS). Drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias, including Torsades de pointes. Therefore concomitant use of these products is not recommended. Examples include certain antiarrhythmics, such as those of Class 1A (such as quinidine, disopyramide and procainamide) and Class III (such as amiodarone, sotalol and dofetilide), certain antimicrobials (sparfloxacin, moxifloxacin, erythromycin IV), tricyclic antidepressants (such as amitriptyline), certain tetracyclic antidepressants (such as maprotiline), other neuroleptics (e.g. phenothiazines, pimozide, sertindole and haloperidol), certain antihistamines (such as terfenadine), cisapride, bretylium and certain antimalarials such as quinine and mefloquine. Drugs causing electrolyte imbalance are not recommended. Diuretics, in particular those causing hypokalemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred. Increased risk of seizures when co-administered with valproic acid. Highly protein bound drugs e.g. warfarin and digoxin may increase in plasma concentration. Phenytoin may cause a decrease in the DENZAPINE plasma concentrations. **Undesirable effects** Adverse reactions are ranked under headings of frequency, using the following convention: Very common (1/10), common (1/100, < 1/10), uncommon (1/1,000, < 1/100), rare (1/10,000, < 1/1,000), very rare (< 1/10,000), including isolated reports. **Blood and lymphatic system disorders** Common: Leucopoenia/decreased WBC/neutropenia, eosinophilia, leukocytosis, Uncommon: Agranulocytosis, Rare: Anaemia, Very rare: Thrombocytopenia, Thrombocythaemia. **Metabolism and nutrition disorders** Common: Weight gain, Rare: Impaired glucose tolerance, diabetes mellitus, Very rare: Ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypertriglyceridaemia, hypercholesterolaemia. **Psychiatric disorders** 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, Rare: Confusion, delirium, Very rare: Tardive dyskinesia. **Cardiac disorders** Very common: Tachycardia, Common: ECG changes, Rare: Circulatory collapse, Ventricular arrhythmias (VF, VT), myocarditis, pericarditis/pericardial effusion, Very rare: Cardiomyopathy, cardiac arrest, QT prolongation, Torsades de pointes. **Vascular disorders** Common: Hypertension, postural hypotension, syncope, Rare: Thromboembolism. **Respiratory disorders** Rare: Aspiration of ingested food, Very rare: Respiratory depression/arrest. **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. **Hepatobiliary disorders** Common: Elevated liver enzymes, Rare: Hepatitis, cholestatic jaundice, pancreatitis, Very rare: Fulminant hepatic necrosis. **Skin and subcutaneous tissue disorders** Very rare: Skin reactions. **Renal and urinary disorders** Common: Urinary incontinence, urinary retention, Very rare: Interstitial nephritis. **Reproductive system disorders** Very rare: Priapism. **General disorders** Common: Fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation, Uncommon: Neuroleptic malignant syndrome, Very rare: Sudden unexplained death, Rare: Increased CPK for further information about side effects refer to the full Summary of Product Characteristics. **Package Quantities and Price - UK Price:** 84 x 25mg tablets £16.64, 100 x 25mg tablets £19.80,84 x 100mg tablets £66.53, 100x100mg tablets £79.20,100ml x 50mg/ml £39.60. Supply of DENZAPINE is restricted to pharmacies registered with the DMS. **Product Licence Numbers** DENZAPINE 25 mg tablets PL04483/0071; DENZAPINE 100 mg tablets PL06831/0267; and DENZAPINE 50mg/ml suspension PL06831/0270. **Legal Category** POM. **SmPC Revision Date** January 2012. **API Revision Date** December 2014. **Marketing Authorisation Holder in the UK** Britannia Pharmaceuticals, 200 Longwater Avenue, Green Park, Reading, Berkshire, RG2 6GP

Full prescribing information and further information is available from Britannia Pharmaceuticals on 0870 851 0207.

Adverse events should be reported. Reporting forms and information can be found at www. mhra.gov.uk/yellowcard Adverse events in the UK should also be reported to Britannia Pharmaceuticals at the address above or on 0870 851 0207.

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