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CLOZARIL ABBREVIATED PRESCRIBING INFORMATION. Please see Summary of Product Characteristics (SPC) before prescribing Clozaril. The use of Clozaril is restricted to patients, physicians and nominated pharmacists registered with the Clozaril Patient Monitoring Service (CPMS). White cell count with differential count must be monitored according to the Irish Official Recommendations. Indications: Treatment-resistant schizophrenia and patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including an atypical antipsychotic agent prescribed for adequate duration. Psychotic disorders occurring during the course of Parkinson's disease, where standard treatment has failed. **Presentations:** 25mg and 100mg clozapine tablets. **Dosage and Administration:** *Treatment-resistant schizophrenic patients.* 12.5 mg once or twice on the first day, followed by 25 mg tablets once or twice on the second day. Increase dose slowly, by increments (see Summary of Product Characteristics (SPC). In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. If dose does not exceed 200mg/day, it can be given as a single administration in the evening. Once control is achieved, a lower maintenance dose may be effective. Treatment should be maintained for at least 6 months. Doses up to 900mg/day can be used but the possibility of increased adverse events especially seizures must be considered. See SPC for details on re-starting therapy, ending treatment or switching from another antipsychotic. Elderly: Initiate at 12.5 mg once on the first day, with subsequent dose increments restricted to 25 mg/day. Children and Adolescents: Children and adolescents under the age of 16 should not use Clozaril due to the lack of data on safety and efficacy. *Psychotic disorders occurring during the course of Parkinson's disease.* The starting dose must not exceed 12.5 mg/day taken in the evening. Increase dose by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, preferably given as a single dose in the evening. The mean effective dose is usually between 25 and 37.5 mg/day. The maximum dose of 100 mg/day must never be exceeded. Dose increases should be *limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs.* Blood pressure should be monitored during the first weeks of treatment. When there has been complete remission of psychotic symptoms for at least two weeks, an increase in anti -parkinsonian medication is possible on the basis of motor status. See SPC for information on ending therapy. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. 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 Clozaril induced agranulocytosis. Impaired bone marrow function. Uncontrolled epilepsy. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions. Circulatory collapse and/or CNS depression of any cause. Severe renal or cardiac disorders (e.g. myocarditis). Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure. Paralytic ileus. Concurrent treatment with substances known to have a substantial potential for causing agranulocytosis. Concomitant use of depot antipsychotics is discouraged. **Warnings and Precautions:** Before initiating clozapine therapy, patients should have a blood test and a history and physical examination. Clozaril can cause agranulocytosis, so is restricted to patients who have initially normal leukocyte findings. (White Blood Cell (WBC) count ≥3.5 x 10^9/l and Absolute Neutrophil Count (ANC) ≥2.0 x 10^9l), and in whom regular WBC counts and ANC can be performed within 10 days prior to starting Clozaril, weekly for first 18 weeks, thereafter at 4 week intervals throughout treatment and for 4 weeks after complete discontinuation. Patients with history of cardiac illness or abnormal cardiac findings on physical examination prior to treatment 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. Prior to treatment initiation, physicians must ensure that the patient has not experienced an adverse haematological reaction to clozapine that necessitated discontinuation. Immediate discontinuation of Clozaril is mandatory if either the WBC count is less than 3.0 x 10^9/l or the ANC is less than 1.5 x 10^9/l at any time during Clozaril treatment. Patients in whom Clozaril has been discontinued as a result of either WBC or ANC deficiencies must not be re-exposed to Clozaril. Following discontinuation of Clozaril, haematological evaluation is required until haematological recovery has occurred. If Clozaril has been withdrawn and either a further drop in the WBC count below 2.0 x 10^9/l occurs or the ANC falls below 1.0 x 10^9/l the management of this condition must be guided by an experienced haematologist. The patient should be educated to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. WBC and differential blood counts must be performed immediately if any symptoms or signs of an infection occur. If, during Clozaril therapy, either the WBC count falls to between 3.5 x 10^9/l and 3.0 x 10^9/l or the ANC falls to between 2.0 x 10^9/l and 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 3.0-3.5 x 10^9/l and 1.5-2.0 x 10^9/l respectively, or higher. Discontinuation of Clozaril is recommended if the eosinophil count rises above 3.0 x 10^9/l; therapy should be restarted only after the eosinophil count has fallen below 1.0 x 10^9/l. Discontinuation of Clozaril therapy is recommended if the platelet count falls below 50 x 10^9/l. Orthostatic hypotension, with or without syncope, can occur during Clozaril treatment. Rarely, collapse can be profound and may be accompanied by cardiac and/or respiratory arrest which is more likely to occur with concurrent use of certain medications (See SPC for more details) and during initial titration with rapid dose escalation. Patients starting Clozaril treatment require close medical supervision. Clozaril is associated with an increased risk of myocarditis, pericarditis/pericardial effusion and cardiomyopathy; and if suspected , Clozaril treatment should be promptly stopped and the patient immediately referred to a cardiologist. Patients with clozapine -induced myocarditis or cardiomyopathy should not be re-exposed to Clozaril. 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 or symptoms mimicking myocardial infarction. Flu-like symptoms may also be present. Patients with a history of epilepsy should be closely observed during Clozaril therapy since dose related convulsions have been reported. Patients with stable pre-existing liver disorders or liver dysfunction need regular liver function tests. If the LFT is elevated, discontinue Clozaril and resume only if LFTs return to normal. Use with care in patients with a history of colonic disease, a history of lower abdominal surgery, glaucoma, narrow angle glaucoma, prostatic enlargement and in patients receiving concomitant medications known to cause constipation. High temperatures should be evaluated carefully to rule out underlying infection, agranulocytosis or Neuroleptic Malignant Syndrome. Patients with rare hereditary problems of galactose intolerance, should not take Clozaril. Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. Immobilisation of patients should be avoided due to reports of thromboembolism. Caution when prescribing to pregnant women. Mothers receiving Clozaril should not breast-feed. Adequate contraceptive measures must be ensured in women of childbearing potential. Activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment. **Interactions:** Clozaril must not be used concomitantly with substances having a well known potential to suppress bone marrow function. (See Section 4.3 of the SPC, Contraindications). Long-acting depot antipsychotics (with myelosuppressive potential) must not be used with Clozaril because these cannot be removed from the body in situations where they may be required e.g. neutropenia. Alcohol should not be used with Clozaril due to possible potentiation of sedation. Caution is advised if Clozaril is used concomitantly with other CNS active agents such as, MAOIs, SSRIs especially fluvoxamine, caffeine, CNS depressants including narcotics, antihistamines and benzodiazepines, Caution is advised if Clozaril is used concomitantly with antihypertensive agents, highly protein bound drugs (e.g. warfarin and digoxin), phenytoin, lithium, rifampicin, valproic acid, noradrenaline [norepinephrine], adrenaline [epinephrine] or omeprazole. 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 In cases of sudden cessation of smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects. See SPC for more details. **Undesirable Effects:** Adverse reactions are ranked under headings of frequency. 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. **Very common:** Drowsiness/sedation, dizziness, tachycardia, constipation, hypersalivation. **Common:** Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis, weight gain, blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures, convulsions, myoclonic jerks, ECG changes, hypertension, postural hypotension, syncope, nausea, vomiting, anorexia, dry mouth, elevated liver enzymes, urinary incontinence, urinary retention, fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation. **Uncommon:** Agranulocytosis, neuroleptic malignant syndrome. **Rare:** Thromboembolism, anaemia, impaired glucose tolerance, diabetes mellitus, restlessness, agitation, confusion, delirium, circulatory collapse, arrhythmias, myocarditis, pericarditis/pericardial effusion, aspiration of ingested food, dysphagia, hepatitis, cholestatic jaundice, pancreatitis, increased CPK. **Very rare:** Thrombocytopenia, thrombocythaemia, ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypertriglyceridaemia, hypercholerolaemia, tardive dyskinesia, cardiomyopathy, cardiac arrest, respiratory depression/arrest, parotid gland enlargement, intestinal obstruction/paralytic ileus/faecal impaction, fulminant hepatic necrosis, skin reactions, interstitial nephritis, priapism, sudden unexplained death. Very rare events of 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. **Package Quantities:** 84 x 25 mg tablets. 84 x 100 mg tablets. Supply of CLOZARIL is restricted to hospital pharmacies registered with the CLOZARIL Patient Monitoring Service. **Product Authorisation Numbers:** 25 mg tablets: PA 13/46/1. 100 mg tablets: PA 13/46/2. **Product Authorisation Holder:** Novartis Pharmaceuticals UK Ltd., Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR, United Kingdom. **Legal Category:** POM. **Date of last revision:** April 2009. CLOZARIL is a registered Trade Mark **Full prescribing information, including Summary of Product Characteristics, is available from:** Novartis Ireland Ltd., Beech House, Beech Hill Office Campus, Clonskeagh, Dublin 4. Tel: 01-2601255. Date of Preparation: February 2010. NO0210043.

* Clozaril Patient Monioring Service (CPMS) Customer Satisfaction Survey October 2009.

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