CLOZAPINE

Information for General Practitioners for use in Schizophrenia

NB – this not a shared care document

General Statements

- Clozapine is a RED drug - patient will always receive supplies of this drug from a hospital unit.
- Clozapine must be initiated in secondary care under specialist supervision.
- This drug is licensed for treatment-resistant schizophrenia.
- Treatment resistant schizophrenia is defined as failure to respond to two or more sequential uses of antipsychotic monotherapy (one of which should be an atypical antipsychotic) each at an adequate dose for at least 6-8 weeks.
- Although the GP will not have prescribing responsibilities, this document highlights some areas of concern of which the GP should be aware.

Background

- Schizophrenia is one of the most common of the severe mental health illnesses.
- Evidence shows that drug treatment with antipsychotics forms an important part of the care programme of patients with schizophrenia.
- Around 30% of patients will not respond adequately to conventional or atypical antipsychotics.
- The evidence base suggests that a large proportion of this group can be successfully treated with clozapine.
- Treatment with clozapine will only be commenced by a consultant psychiatrist after determining that the patient is treatment-resistant.

Pharmacological Summary

Clozapine has only weak dopamine-receptor-blocking activity at D1, D2, D3 and D5 receptors but shows high potency for D4 receptors. In addition it has potent anti-alpha adrenergic, anticholinergic and antihistaminic activity. It also has antiserotonergic properties

Dosage and Administration

- Clozapine should generally be prescribed as the sole antipsychotic, although there is some evidence for augmentation with risperidone, amisulpride, sulpiride or aripiprazole in resistant cases.
- Usually twice daily dosage.
- Initially clozapine is titrated from 12.5mg daily to a dose of 100mg mane and 200mg nocte over 16 days. If the patient misses more than 48 hours of doses at any time, it **must** be re-titrated to the original dose.
- Usual dose range is 200mg – 450mg per day, maximum dose is 900mg per day.
- Patients will have FBCs performed whenever they are taking clozapine. The frequency of testing is weekly for the first 18 weeks of therapy, fortnightly for the remainder of the first year and four week intervals thereafter.

Adverse Effects

- **Agranulocytosis**. 1-2% of patients may suffer neutropenia leading to agranulocytosis. Regular FBCs are conducted for all patients taking clozapine, coordinated by a centralised monitoring service.
- The drug does not generally cause EPSE which is often seen with conventional antipsychotics.
- Neuroleptic malignant syndrome (NMS) has occurred. If suspected cease treatment and refer for specialist advice.
- Drowsiness and sedation are commonly reported.
- Hypersalivation is commonly seen, despite significant anticholinergic properties.
- Weight gain was experienced by greater than 10% of clinical trials patients.
- There have been some reports of clozapine causing altered glucose tolerance. Patients at risk of diabetes should have their plasma glucose levels checked.
- Myocarditis or cardiomyopathy should be suspected in patients who experience 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. In these cases clozapine should be promptly stopped and the patient immediately referred to a cardiologist and their psychiatrist.
- Constipation. It is vital that constipation is recognised and actively treated.
- As with other antipsychotics there is a potential for tardive dyskinesia with long term treatment.

Precautions and Contra-indications

- **Pregnancy** — No teratogenic effects have been noted but safety in pregnancy has not been established. It is recommended that you contact the Medicines Information Department at your local hospital for the most up to date information and advice.
- **Breast feeding** Avoid as no information is available.
- **Hyperglycaemia** — Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for developing diabetes mellitus.
- **Epilepsy** — As with other antipsychotics caution is recommended when treating patients with a history of seizures as convulsive threshold may be lowered.
- **Prostatic enlargement. Narrow-angle glaucoma** — Due to anticholinergic properties of clozapine careful supervision is required in these conditions.
- **Depot antipsychotics** and risperidone long acting injection are contraindicated in combination with clozapine.
- **QTC prolonging drugs-e.g. escitalopram, citalopram-** will need to monitor ECG closely, please seek further advise from the contact details below, if necessary.

Clinically Relevant Drug Interactions and their Management

- Smoking may induce the metabolism of clozapine, resulting in reduced plasma clozapine levels.
- Sudden smoking cessation may increase plasma clozapine levels and may lead to adverse effects; a dose adjustment of clozapine may be required.
- Caffeine can increase plasma clozapine levels. A change in caffeine drinking habit may require an adjustment of the clozapine dose**.**
- **Clozapine is contraindicated with other drugs known to have a substantial potential to cause agranulocytosis, e.g., carbamazepine, oxcarbazepine, penicillamine, chloramphenicol (not topical), any chemotherapy regimen,** in addition to **methotrexate** when used in rheumatology settings.

- Cytochrome P450-1A2 inhibitors such as fluvoxamine, ketoconazole, erythromycin, clarithromycin and ciprofloxacin can inhibit the metabolism of clozapine, resulting in raised plasma levels. The antidepressants fluoxetine, paroxetine, and venlafaxine may also cause elevated plasma levels; citalopram and sertraline may do to a lesser extent.
- Cytochrome P450-1A2 inducers such as omeprazole may lead to decreased clozapine levels.
- Use with caution in combination with other centrally acting drugs.
- Anticholinergics — Due to additive anticholinergic activity with clozapine observe patient for side-effects (e.g. constipation).
- Benzodiazepines — Occurrence is rare, but concomitant use may increase the risk of circulatory collapse. Therefore on initiation monitoring of blood pressure, temperature, pulse and respiratory rate is advised.
- Sedating drugs –can compound the sedating effects of clozapine.
- Some antibiotics can increase the risk of neutropenia e.g. trimethoprim, metronidazole, nitrofurantoin, cephalexin and cephradine.
- Highly protein bound drugs -clozapine can increase the effect of e.g. warfarin, digoxin.
- Antihypertensives- clozapine may potentiate the effect of antihypertensives

Responsibilities of Each Participating Partner

Secondary Care

- Initiation of treatment and **all** prescribing of clozapine.
- Baseline monitoring of clinical parameters.
- Ongoing monitoring of physical health and side effects.
- Discussion of risks and benefits of medication with patients and carers.
- Monitoring of efficacy and tolerance of clozapine, and oversight of continued FBC testing.

Primary care

Clozapine patients will almost certainly be on your SMI register and so will be having their physical health monitored. You may also wish to consider;

- Discussion of risks and benefits of medication with patients and carers.
- To be alert to complaints of flu-like symptoms or other evidence of infection this may be indicative of neutropenia. An immediate differential blood count must be obtained if these symptoms develop.
- To check the compatibility of all co-prescribed medications with clozapine. Further advice on this, *or any other topic,* can be obtained from the contact details below.

When and How to Discontinue Treatment

Discontinuation will usually be managed by Secondary Care. Gradual discontinuation is generally recommended to avoid the risk of acute withdrawal syndromes or rapid relapse. If the patient stops the medication without medical advice please refer immediately to Secondary Care.

What Information the Patient has been given

- The patient will be involved in the choice of medication and written information given, and will be advised about the necessity for continuing full blood counts.
- A patient information leaflet will be given to the patient with the medication.

Patient Information to be received by the GP from Secondary Care

- Diagnosis.
- Details of preparation and dose regimen for clozapine
- Concurrent medication prescribed via secondary care.

- Details of patient follow up including care plan.
- Details of any identified problems e.g. compliance and treatment.
- Details of mental health key worker if appropriate.

Patient information which the GP may wish to pass to the Consultant

- Details of concurrent medication.
- Details of any identified problems e.g. compliance with treatment.
- Details of any deterioration in the mental or physical state.

Preparations

- Available as Tablets 25mg and 100mg from Novartis, Teva UK and Merz.
- Available as Suspension 50mg/ml from Merz

Contact Details

, Tel:

Clozapine Clinic, Tel: