# This document must be filed prominently in the patient's primary care notes
# Clozapine (Zaponex®) for GPs and other health professionals

A medicine for schizophrenia and psychosis in Parkinson's disease

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**Ensure that clozapine is added to the electronic patient's medication list (GP) but not for issuing** (appendix 2)
Add patient to the mental health register (GP)
Perform annual primary care review (GP)
Urgent full blood count if signs of infection inc. sore throat & flu symptoms
**Clozapine can cause constipation- RISK OF FATALITY. Act promptly and treat actively when constipation is recognised: if untreated may lead to fatal complications (appendix 1)**
Do not restart if there has been a break of >48h between doses
Check drug interactions
Stopping smoking can increase clozapine levels; be alert to smoking status
Increased risk of myocarditis or cardiomyopathy may be fatal in rare cases

This document provides important information with respect to the prescribing of clozapine. Clozapine is prescribed, monitored and supplied by the hospital and CMHT, not the GP. **However, familiarity with the contents of this document will serve to protect patients treated with clozapine from adverse events associated with its use.**

Clozapine has been shown to be the drug treatment of choice in treatment resistant schizophrenia. It may also be prescribed for patients with schizophrenia who are intolerant of other antipsychotic drug treatment or for patients with psychosis in Parkinson's disease when other treatment strategies have failed.[1]

The Zaponex® brand of clozapine is prescribed in Derbyshire Healthcare Trust. Response rates to clozapine in patients with refractory schizophrenia are reported to be 30% at 6 weeks and 60% at one year. For most patients, efficacy can be expected with doses between 200 to 450mg a day (in divided doses); the maximum licensed dose is 900mg/day. Studies have shown as much as a 45-fold inter-individual difference in plasma levels for the same dose, hence individuals can vary greatly in their experience of side effects and tolerability of a specific dose [2]

## Dose initiation and breaks in treatment

Since many of the adverse effects of clozapine are dose-dependent and associated with speed of titration, therapy is started at a low dose (12.5mg once a day) and increased slowly. If the patient has not taken clozapine for more than **48 hours** advise that the usual dose **must not** be resumed. The psychiatrist must be contacted urgently as the dose must be re-titrated from 12.5mg/day. Please report any concerns regarding non-adherence with treatment to the psychiatrist.

## Monitoring

All patients receiving clozapine in Derbyshire must be monitored physically by the community team as per the Trust's monitoring guidelines for antipsychotics. In addition, white cells and neutrophils are checked each week, fortnight or 4-weeks depending on the specification of the Zaponex Treatment Access System (ZTAS). Clozapine increases the incidences of diabetes and cardiac events in a group already at increased risk.

**GPs should liaise with the mental health team if there are any identified physical health concerns that may impact on treatment.**

**Adverse effects** 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.

| Adverse effect[1] | Incidence[1] | Action |
|---|---|---|
| Anticholinergic effects-**constipation** | **Very common** | **Act promptly and treat actively when constipation is recognised. This side effect must not be ignored. Constipation can lead to clozapine toxicity and deaths have occurred as a result of paralytic ileus and perforation. See appendix 1** |
| dry mouth | Common | Advise symptomatic relief. May be a sign of too high dose, consider informing psychiatrist |
| blurred vision | Common | May be a sign of too high dose, consider informing psychiatrist. Careful supervision is indicated in the presence of narrow-angle glaucoma. |
| urinary retention (incontinence can also occur) | Common | Manage in consultation with psychiatrist and urologist. Acute retention may need emergency catheterisation and hospital admission. |
| Pyrexia (Agranulocytosis/neutropenia, Neuroleptic malignant syndrome (NMS), myocarditis, Infection/pneumonia) | Common | During clozapine therapy, patients may experience transient temperature elevations above 38ºC, especially within the first 3 weeks of treatment. This fever is generally benign. Occasionally it may be associated with an increase or decrease in the WBC count. **Take urgent full blood count with differential** If serious causes can be excluded, clozapine therapy may be continued. In the presence of high fever consider the possibility of neuroleptic malignant syndrome (NMS) and stop clozapine if confirmed. |
| Hypersalivation | Very common | Extra pillows at night/daytime chewing gum may help[8]. Liaise with specialist to consider dose reduction. May be treated with hyoscine hydrobromide (Kwells); suck and swallow a 300mcg tablet up to three times a day. Unlicensed. |
| Sedation | Very common | Manipulation of dosage times may alleviate daytime sedation. Dose may be too high. Inform psychiatrist. |
| Hypertension, postural hypotension, syncope | Common | Dose may have been increased too quickly or dose is too high. Inform psychiatrist. |
| Tachycardia[4] (see myocarditis/cardiomyopathy) | Very common | More common at beginning of treatment. Exclude myocarditis, cardiomyopathy or NMS. Dose may have been increased too quickly or dose is too high. Inform psychiatrist. Where persistent and clinically appropriate consider management with a low dose beta-blocker e.g. bisoprolol. |
| Weight gain | Common | Lifestyle advice. Referral to dietician may be appropriate. Ensure physical monitoring as per the monitoring guidelines for antipsychotics (e.g. glucose, lipids). |
| Seizures/convulsions/myoclonic jerks | Common | More common with higher doses of clozapine. May be a sign of toxicity. Inform psychiatrist immediately. |
| Agranulocytosis/neutropenia (patient may report symptoms of infection e.g, flu-like symptoms, sore throat, high temperature) | Uncommon / common | Urgent full blood count indicated. Inform psychiatrist immediately. Clozapine to be discontinued if WCC<3.0x$10^9$/L or ANC<1.5x$10^9$/L. |
| Myocarditis/Cardiomyopathy | Rare/Very rare | If myocarditis or cardiomyopathy suspected clozapine should be stopped and patient referred to cardiologist. Suspect in patients who have persistent tachycardia at rest, particularly during the first two months, palpitations, arrhythmias, chest pain, and other signs/symptoms of heart failure or symptoms that mimic MI. Fever or flu-like symptoms may also be present. Inform psychiatrist. |

## Smoking[5]

Smoking tobacco reduces plasma levels of clozapine by up to 50% so smokers may need higher doses. Likewise, patients who stop smoking may experience a significant increase in plasma level; there have been case reports of adverse effects in patients taking clozapine when they have stopped smoking. This effect is related to inhalation of tobacco smoke and is **independent of any NRT product** used including e-cigarettes (vape).

If your patient wants to quit/cut down smoking inform the psychiatric team so that a dose reduction can be considered before quitting/cutting down. Side effects of clozapine should be reviewed regularly during the period of cutting down.

## Interactions

Clozapine is contraindicated with

- other medicines with a substantial potential to depress bone marrow function (e.g. carbamazepine, carbimazole).

Clozapine is cautioned with

- other medicines with anticholinergic effects (additive effect) e.g. some drugs for urinary incontinence - be aware of potential additive constipation burden
- other medicines with hypotensive effects (additive effect)
- erythromycin and ciprofloxacin; may increase clozapine levels and are associated with additive QTc risks[7]
- alcohol, due to potential for sedation
- benzodiazepines, due to increased risk of circulatory collapse.
- Medicines which decrease clozapine levels eg omeprazole

Try to avoid antibiotics with potential to cause e.g. blood dyscrasias eg trimethoprim and nitrofurantoin.[7]
This is not an exhaustive list. Please see BNF and summaries of product characteristics for further information.

## Contacts

| Consultant Psychiatrist | Community Team & Care Coordinator | Pharmacy | Zaponex Treatment Access Service (ZTAS) |
|---|---|---|---|
| | | Ashbourne Centre, Kingsway<br>01332 623700 | emergency medical contact<br>Tel: 020 7365 5842 (UK) |

## References


1. Summary of Product Characteristics. Leyden Delta BV. www.medicines.org.uk/emc Accessed 8th March 2022
2. Zaponex Fact Sheet: clozapine metabolism and plasma level monitoring https://www.ztas.com accessed 8th March 2022 (user ID and password required) (user id and password required)
3. Zaponex Fact Sheet: Fever https://www.ztas.com accessed 8th March 2022 (user ID and password required)
4. 'Zaponex Fact Sheet: Tachycardia https://www.ztas.com accessed 8th March 2022 (user ID and password required)
5. Medicines Q&As: What are the clinically significant drug interactions with cigarette smoking? July 2020 www.sps.nhs.uk accessed online 8th March 2022
6. Stockley's drug interactions www.new.medicinescomplete.com accessed 9th March 2022 (password required)
7. Zaponex Fact Sheet: Hypersalivation https://www.ztas.com accessed 8th March 2022 (user ID and password required)

## Appendix 1 - Clozapine and constipation- advice for GP

Clozapine is associated with gastrointestinal hypomotility. In studies about 50-80% of patients showed objective evidence of slowed colonic transit. In some cases this can lead to paralytic ileus, bowel obstruction, bowel ischaemia and necrosis and can be life-threatening.

Although clozapine is managed by secondary care, patients treated with clozapine may present in Primary care with constipation. It is vital that these patients are promptly and effectively treated.

Clozapine patients and carers are reminded of the symptoms that suggest urgent help is needed and given a copy of the Choice and Medication handy fact sheet 'clozapine and constipation'.

**Management of constipation**
In patients taking clozapine (or who will be prescribed clozapine) the recommendations are as follows:

First line: docusate plus senna
Second line: add macrogol (e.g. laxido)
If no response, refer for gastroenterologist review.

(Notes: Lactulose is not recommended due to requirement to maintain high fluid intake and delay in time to effect. Avoid ispaghula/fybogel – unsuitable where there is slow transit time/risk of obstruction).

**See Derbyshire formulary chapter 1 (Link) for further detail on assessment and management of constipation in adults**

## Appendix 2

**Guidance for adding medicines prescribed and issued by other HCPs to GP clinical systems**

It is essential that practices' clinical systems make users unambiguously aware of patients who are prescribed clozapine. Practices should take appropriate steps to ensure that this information is clearly visible within the patient record.

Local 'Recording medicines prescribed and issued by other Healthcare Providers on GP clinical systems' guidance suggests methods of achieving this, although the nature of implementation might vary between systems and between practices depending on local policy.