This Safety Notice highlights possible Clozapine toxicity related to smoking cessation or reduction.

**Background**

Case reports have described symptoms of Clozapine toxicity following smoking cessation or reduced smoking.
- Clozapine has a narrow therapeutic index and significant toxic side effects.
- Clozapine is metabolised in the liver by the cytochrome P450 system.
- Tobacco smoke induces P450 1A2 activity, affecting Clozapine metabolism.
- Smokers require higher doses of Clozapine than non-smokers.
- Smoking cessation leads to a rapid decrease in cytochrome P450 activity.
- This can lead to rapid rises in blood levels of Clozapine and toxic effects.
- There should be an immediate decrease of Clozapine dose on cessation of smoking.

Note: it is the components of tobacco smoke and not nicotine that induce P450 1A2.

**Signs of increased blood levels / toxic effects**

- sedation
- hypotension
- hypersalivation
- akathisia
- neurological adverse effects including seizures

Note: Other toxic effects, including agranulocytosis, are not dose related.

**Steps to minimise risk**

- Ask about smoking status (current smoker or recently quit) and current Clozapine dosage;
- Measure and record baseline Clozapine levels;
- Consider a dose reduction of 30-50% if the consumer stops smoking;
- Clinically monitor for effectiveness and toxicity; and
- Discuss the impact of smoking on Clozapine levels with the consumer; and inform other carers and GP.

Note: Clozapine levels start to rise within 24 hours of smoking cessation or reduction.

**References**


**Suggested Actions by Local Health Districts/Networks:**

1. Ensure this safety notice is distributed to all relevant staff to ensure they are aware of the symptoms potentially associated with the consumption of Clozapine.
2. Ensure a system is in place to document actions taken.