Dear Healthcare Professionals,

**Clozapine and other antipsychotics: monitoring blood concentrations for toxicity**

Your attention is drawn to the Medicines and Healthcare products Regulatory Agency’s (MHRA) announcement that blood level monitoring of clozapine and other antipsychotic medicines can be beneficial in the care and management of patients, particularly those with treatment-resistant conditions. For example, monitoring of blood clozapine levels may be useful when a patient starts (or restarts) smoking as this may lead to a decrease in blood clozapine levels and dose adjustment may be necessary. However, the advice below focuses on drug blood level monitoring for toxicity of clozapine and other antipsychotics.

The MHRA has received 2 separate reports from Coroners raising concerns regarding the need for monitoring of clozapine blood levels in one report and monitoring antipsychotic blood levels during long-term high-dose antipsychotic use in the other. In the first report, the individual’s death was determined to have been caused by clozapine toxicity, pneumonia, and treatment-resistant schizophrenia. In the second report, the death of a patient on long-term high-dose antipsychotic treatment was determined to have been caused by coronary artery atherosclerosis and amisulpride toxicity. In both Coroner’s reports, the MHRA was asked to take action to prevent further deaths. Expert Advisory Groups of the Commission on Human Medicines considered safety data for clozapine and other antipsychotic drugs and advised that blood concentrations of clozapine should be monitored for toxicity in certain clinical situations. The Groups also advised that, where assays and suggested reference values are available, blood level monitoring of other antipsychotic drugs may be helpful in certain circumstances. At the time of publication, assays and suggested reference values for therapeutic blood concentrations are known to be available for amisulpride, aripiprazole, olanzapine, quetiapine, risperidone and sulpiride, although availability of testing may vary locally.

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Advice for healthcare professionals:
- Monitoring blood clozapine levels for toxicity is now advised in certain clinical situations such as when: a patient stops smoking or switches to an e-cigarette; concomitant medicines may interact to increase blood clozapine levels; a patient has pneumonia or other serious infection; poor (reduced) clozapine metabolism is suspected; toxicity is suspected.
- If blood clozapine level monitoring is carried out, this should be in addition to the required blood tests to manage the risk of agranulocytosis.
- For other antipsychotics, where assays and suggested reference values are available, blood level monitoring for toxicity may be helpful in certain circumstances, for example in the event of symptoms suggestive of toxicity or when concomitant medicines may interact to increase antipsychotic drug levels.
- Refer to the full Summaries of Product Characteristics for other important warnings, interactions, and recommendations for clozapine and other individual antipsychotics.

Please refer to the following website in MHRA for details:

In Hong Kong, there are registered pharmaceutical products containing clozapine (9 products) and other antipsychotic medicines such as amisulpride (15 products), aripiprazole (29 products), olanzapine (57 products), quetiapine (61 products), risperidone (58 products) and sulpiride (10 products). All products are prescription-only medicines. So far, the Department of Health (DH) has received adverse drug reaction related clozapine (3 cases), amisulpride (2 cases), olanzapine (23 cases), quetiapine (6 cases) and risperidone (5 cases). The DH has not received any case of adverse drug reaction related to aripiprazole or sulpiride. The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Undesirable Medical Advertisements and Adverse Drug Reaction Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

(Joseph LEE)
for Assistant Director (Drug)

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