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(IN REPLY PLEASE QUOTE THIS FILE REF.)

Dear Healthcare Professionals,

Apomorphine with domperidone: minimising risk of cardiac side effects

Your attention is drawn to the Medicines and Healthcare products Regulatory Agency's (MHRA) announcement regarding patients receiving apomorphine and domperidone require an assessment of cardiac risk factors and ECG monitoring to reduce the risk of serious arrhythmia related to QT-prolongation.

Apomorphine (brand names: APO-go, Dacepton in the UK) is a dopamine agonist used to treat refractory motor fluctuations in people with Parkinson's disease. Domperidone (brand names: Motilium, Dismotil in the UK) is usually started at least two days before apomorphine to control the expected side effects of nausea and vomiting.

In 2014, a review by EU medicines regulators on risk of cardiac side effects of domperidone concluded that domperidone is associated with a small increased risk of QT-interval prolongation, serious ventricular arrhythmias, and sudden cardiac death. A higher risk was observed in people older than 60 years, people taking daily oral doses of more than 30 mg, and in those taking other QT-prolonging medicines or cytochrome P450 3A4 inhibitors at the same time as domperidone. As a result of this review, the licensed indication for domperidone was restricted to relief of nausea and vomiting, the licensed dose was reduced, and several contraindications were introduced.

Apomorphine can increase the risk of QT-prolongation at high doses. A review by EU medicines regulators of the safety of concomitant apomorphine and domperidone use has recently finished. This review concluded that health professionals should take the precautions listed above to reduce the risk of QT-prolongation. The risk of QT-prolongation may be increased in people on concomitant apomorphine and domperidone who have certain risk factors, including pre-existing QT-interval prolongation, serious underlying cardiac disorders such as heart failure, severe hepatic dysfunction, significant electrolyte disturbances, and concomitant drug therapy that may increase domperidone levels (eg, cytochrome P450 3A4 inhibitors).

The MHRA advised healthcare professionals of the following:

- Before starting treatment, carefully consider whether the benefits of concomitant apomorphine and domperidone treatment outweigh the small increased risk of cardiac side effects
- Discuss the benefits and risks of apomorphine with patients and carers and advise them to contact their doctor immediately if they develop palpitations or syncopal symptoms during treatment
- Check the QT-interval before starting domperidone, during the apomorphine initiation phase and if clinically indicated thereafter (eg, if a QT-prolonging or interacting drug is started or if symptoms of cardiac side effects are reported)
- Regularly review domperidone treatment to ensure patients take the lowest effective dose for the shortest duration

- Advise patients to inform their doctor of any changes that could increase their risk of arrhythmia, such as:
  - symptoms of cardiac or hepatic disorders
  - conditions that could cause electrolyte disturbances (eg, gastroenteritis or starting a diuretic)
  - starting any other medicines.

Please refer to the MHRA's website for details:

https://www.gov.uk/drug-safety-update/apomorphine-with-domperidone-minimising-risk-of-cardiac-side-effects

In Hong Kong, there are three registered pharmaceutical products containing apomorphine, namely Apo-go Solution for Inj 10mg/ml (HK-58095), Apo-go PFS Solution for Infusion 5mg/ml (HK-58096) and Apo-go Pen Solution for Injection 10mg/ml (HK-61219), and 46 registered pharmaceutical products containing domperidone. All products are prescription only medicines. News on the risk with the concomitant use of domperidone and apomorphine has not been previously reported. So far, DH has not received any adverse drug reaction case related to the concomitant use of domperidone and apomorphine. In view of the above MHRA, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board. 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 Pharmacovigilance 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,

(Grant NG)
for Assistant Director (Drug)