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17 Nov 2020

Dear Healthcare Professionals,

Bupropion (Zyban): risk of serotonin syndrome with use with other serotonergic drugs

Your attention is drawn to the United Kingdom Medicines and Healthcare products Regulatory Agency's (MHRA) announcement that cases of serotonin syndrome have been identified in associated with bupropion, especially in overdose or when bupropion is administered with other drugs with a serotonergic effect.

A recent European review of safety data for Zyban identified at least 8 cases of serotonin syndrome, a potentially life-threatening condition, where a possible interaction between bupropion and a serotonergic drug was thought to have led to serotonin syndrome. The review also identified 6 cases with good evidence of an association with an overdose of bupropion. In the majority of these cases the patients had intentionally taken more than the prescribed dose.

The product information has been updated to include post-marketing reports of serotonin syndrome when bupropion is co-administered with a serotonergic agent such as selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine re-uptake inhibitors (SNRIs). If concomitant treatment with other serotonergic agents is clinically warranted, the patient should be advised of the milder symptoms of serotonin syndrome and told to seek advice should they occur, particularly during treatment initiation and dose increases. Advice that serotonin syndrome has been reported in cases of overdose also been included in the product information.

In the United Kingdom up to Oct 2020, the Yellow Card scheme has received 3 reports of serotonin syndrome associated with bupropion, one of which was a potential overdose of bupropion and two of which were associated with concomitant use of antidepressant medicines.

Serotonin syndrome is an iatrogenic disorder of serotonergic hyperstimulation in which the underlying mechanism is thought to involve excessive stimulation of 5-HT1A receptors. It occurs most commonly

when two or more serotonergic agents with different pharmacological mechanisms are administered either concurrently or sequentially without a sufficient washout period. However, it can also be associated with a single serotonergic agent, particularly at a high dose. Signs and symptoms of serotonin syndrome may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyperreflexia, incoordination, rigidity), and gastrointestinal symptoms (e.g. vomiting, diarrhoea). If serotonin syndrome is suspected, a dose reduction or discontinuation of bupropion therapy should be considered, depending on the severity of the symptoms.

Advice for healthcare professionals:

- Cases of serotonin syndrome have been reported in association with bupropion and coadministration with serotonergic drugs, e.g. SSRIs, SNRIs.
- If concomitant prescribing with other serotonergic drugs is clinically warranted: do not exceed the recommended dose; remind patients of the milder symptoms of serotonin syndrome at initiation of treatment and at any change of dose and the importance of seeking medical advice if they occur.
- If serotonin syndrome is suspected, either decrease the dose of bupropion or withdraw therapy depending on the severity of the symptoms.

Please refer to the following website in MHRA for details:
https://www.gov.uk/drug-safety-update/bupropion-zyban-risk-of-serotonin-syndrome-with-use-with-other-serotonergic-drugs

In Hong Kong, there are 5 registered pharmaceutical products containing bupropion, and all products are prescription-only medicines. So far, the Department of Health (DH) has received 4 cases of adverse drug reaction related to bupropion. In light of the above MHRA's announcement, 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 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)