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# WHO Pharmaceuticals NEWSLETTER

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***WHO Vision for Medicines Safety***

***No country left behind: worldwide pharmacovigilance for safer medicines, safer patients***

*The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of national pharmacovigilance centres and other sources such as specialized bulletins and journals, as well as partners in WHO.*

*The information is produced in the form of résumés in English, full texts of which may be obtained on request from:*

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The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities around the world. It also provides signals based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®.

This newsletter includes three feature articles describing: Introduction of an electronic system for reporting adverse drug reactions in Tanzania, Third WHO Asia Pacific Pharmacovigilance Training Course, and Recommendations from the 39th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring.

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## Regulatory Matters



## Safety of Medicines

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## Amiodarone (intravenous)

### Risk of adverse effects of the heart in newborns

**Canada**. Health Canada has requested manufacturers to update the product information for intravenous amiodarone products to include heart risks in new-borns. Although this information is already mentioned for adult patients, it is important that health-care professionals recognize potential risks in newborns and infants.

Amiodarone is used to treat arrhythmias in adults. It is also prescribed by some doctors for the treatment of life-threatening arrhythmias in foetuses and newborns when other medications have not worked.

Health Canada reviewed the potential risk of adverse effects in foetuses and newborns with intravenous amiodarone following an update of product label in the United States which included warnings about potential effects on the heart, nervous system and development and growth of foetuses and newborns.

At the time of the review, Health Canada received three Canadian reports and retrieved 12 additional reports from the published literature of serious adverse effects of the heart including potentially fatal heart attacks in new-borns who received amiodarone for life-threatening abnormal heart rhythms. In 13 of the 15 reports reviewed, it was determined that amiodarone may have played a role in the development of adverse effects.

Results of a published study investigating amiodarone use in children suggested that the risk of hypotension, bradycardia and atrioventricular block may be greater in children than in adults exposed to amiodarone.

Hypothyroidism can be caused by amiodarone exposure *in utero* and is a known cause of developmental delays (such as in learning, speech, and movement) if untreated. However, some children have had developmental delays following amiodarone exposure despite having normal levels of thyroid hormone.

Health Canada's review of the available information did not establish a link between the use of amiodarone during pregnancy and the risk of developmental delays in new-borns but did find a possible link to adverse effects on the heart.

***Reference:***
Summary Safety Review, Health Canada, 6 January 2017 (*www.hc-sc.gc.ca*)

## Bisphosphonates (intravenous)

### Risk of osteonecrosis of the jaw

**Canada**. Health Canada has worked with manufacturers to update safety information of intravenous bisphosphonates products (pamidronate, Zometa®; zoledronate, Aclasta®, clodronate disodium) to reflect the risk of osteonecrosis of the jaw, and to mention the additional factors that may play a role in jaw bone loss for all bisphosphonate products.

Bisphosphonates are used to strengthen bones in a variety of bone-related diseases, such as: osteoporosis; Paget's disease; bone metastases; hypercalcaemia of malignancy; and certain cancers.

There are different kinds of bisphosphonate formulations that can be used orally and/or intravenously.

Health Canada reviewed the potential risk factors of osteonecrosis of the jaw with bisphosphonate use in light of updates to the European product safety information for injectable bisphosphonates.

At the time of the review, Health Canada received 125 unique Canadian reports of jaw bone loss associated with the use of bisphosphonate products. Jaw bone loss was commonly reported in cancer patients.

A review of recent publications and an analysis of the Canadian reports above showed a higher risk of jaw bone loss with the use of bisphosphonates, especially when IV formulations are used compared to oral formulations. Higher doses and strengths as well as longer treatment periods also contribute to the risk.

This review also found other risk factors for jaw bone loss including dental conditions and procedures, radiation therapy, and medical conditions such as anaemia or coagulopathies.

At the time of the review the product information for all bisphosphonates already included a warning about the risk of jaw bone loss, but there were differences in the way the risk was described for the different medicines in this class.

Health Canada's review confirmed the known risk of jaw bone loss with bisphosphonate product use, and further concluded that this risk is higher with intravenous bisphosphonate products, especially in cancer patients.

***Reference:***
Summary Safety Review, Health Canada, 25 November 2016 (*www.hc-sc.gc.ca*)

*(See WHO Pharmaceuticals Newsletters No.4, 2016: Risk of osteonecrosis of external auditory canal in Japan and No1, 2016: Risk of osteonecrosis of the external auditory canal in the United Kingdom)*

## Bupropion and varenicline

### Revision of mental health adverse effects

**USA**. The US Food and Drug Administration (FDA) has

announced that the Boxed Warning for serious mental health adverse effects has been removed from varenicline (Chantix®) product label. Also, the language describing the serious mental health adverse effects seen in patients quitting smoking has been removed from the Boxed Warning in bupropion (Zyban®) label. These updates are based on the results from a review of a large clinical trial which indicate that although the risk of these mental health adverse effects is still present, it is lower than previously suspected.

Bupropion and varenicline are medications used as an aid to smoking cessation treatment.

The FDA has determined that the risk of serious adverse effects on mood, behaviour, or thinking with varenicline and bupropion is lower than previously suspected. The risk of these mental health adverse effects is still present, especially in those currently being treated for mental illnesses such as depression, anxiety disorders, or schizophrenia, or who have been treated for mental illnesses in the past. However, most people who had these adverse effects did not have serious consequences such as hospitalization. The results of the trial confirm that the benefits of stopping smoking outweigh the risks of these medicines.

The FDA review of the clinical trial results has also confirmed that bupropion, varenicline, and nicotine replacement patches were all more effective for helping people quit smoking than placebo. These medicines were found to better help people quit smoking regardless of whether or not they had a history of mental illness.

The patient medication guide that explains the risks associated with the use of the medicines will continue to be provided with every patient prescription; however, the risk evaluation and mitigation strategy (REMS) that formally required the Medication Guide will be removed.

***Reference***:
Drug Safety Communication, US FDA, 16 December 2016 *(www.fda.gov)*

*(See WHO Pharmaceuticals Newsletter No.1, 2016: Risk of psychiatric symptoms by drug-alcohol interaction in Australia)*

## Cajeput Oil (*Melaleuca leucodendran*)

### Risk of glottal spasm and bronchospasm

**Malaysia**: The National Pharmaceutical Regulatory Agency (NPRA) has updated package inserts for cajeput oil containing products to provide information on the risk of glottal spasm and bronchospasm.

Cajeput oil is an essential oil derived from a plant called Kayu Putih (*Melaleuca leucodendran*). It is traditionally used to provide relief of muscle pain, muscle cramps, muscle strains and abdominal discomfort. It is commonly used in infants and small children during post-natal care to provide relief of bloating or abdominal distension, as well as to give warmth after a bath.

From year 2001 to August 2015, the NPRA has received four ADR reports associated with the use of cajeput oil-containing products, all of which involved children aged between eight days to 14 months.

Three of the reports documented three skin adverse drug reactions, namely contact dermatitis, papular rash, and skin hyperpigmentation. One report involved accidental ingestion, in which the patient experienced vomiting.

A literature review has shown that there are warnings of adverse reactions such as glottal spasm, bronchospasm or even asthma-like attacks in paediatric patients when cajeput oil is applied on the face. This could result in breathing difficulties in infants and small children.

The NPRA has advised that preparations containing the oil should not be applied to the faces of infants or small children, as glottal spasm might occur.

***Reference:***
MADRAC Newsletter, National Pharmaceutical Regulatory Agency (NPRA), Malaysia, Vol. 20 August 2016 *(http://npra.moh.gov.my/)*

## Cobicistat, ritonavir and corticosteroid metabolised by CYP3A

### Risk of adrenal suppression due to a pharmacokinetic interaction.

**The United Kingdom**. The Medicines and Healthcare Products Regulatory Agency (MHRA) has strengthened the product information for cobicistat-containing products to warn of the potential interaction with coticosteroids, resulting in systemic corticosteroid-related adverse effects.

Cobicistat is a HIV-treatment-boosting agent and ritonavir is a HIV-protease inhibitor to treat HIV/AIDS.

An EU-wide review has identified eight cases worldwide (including one published report) of adrenal suppression during treatment with a cobicistat-containing regimen (Stribild®) and a subsequent prescription of an inhaled, intranasal, or intra-articular corticosteroid.

Reported adverse reactions were adrenal insufficiency, adrenal suppression and Cushing's syndrome. The corticosteroids involved were intranasal and inhaled

fluticasone, oral budesonide, and intra-articular triamcinolone. From clinical trials, a further report of adrenal insufficiency was identified where epidural methylprednisolone had been used together with intranasal fluticasone.

Up until 21 November 2016, 26 UK Yellow Card reports of an interaction with triamcinolone and ritonavir have been reported: 18 reactions of Cushing's syndrome or cushingoid features, and 17 of adrenal suppression. A separate EU review identified two reports of Cushing's syndrome from interactions between ocular dexamethasone and ritonavir. The review also noted an increased risk of systemic adrenal effects occurring with both ocular and cutaneous use after intensive or long-term therapy, and which were considered to be risk factors for interactions with ritonavir.

The MHRA has highlighted the need: for monitoring patients for adverse events in patients using a corticosteroid metabolised by cytochrome P450 3A (CYP3A) and a HIV-treatment-boosting agent; to consider if the potential benefit to the patient outweighs the risk; and to use lower-risk alternative corticosteroids where possible (particularly, inhaled or intranasal beclomethasone).

***Reference:***
Drug Safety Update, MHRA, Volume 10, issue 5:1, December 2016 *(www.gov.uk/mhra)*

*(See WHO Pharmaceuticals Newsletter No.6, 2016: Potential drug interaction: increased risk of systemic corticosteroid effects with Cobicistat containing products and corticosteroids primarily metabolised by CYP3A in Ireland)*

## Codeine-containing products

### Restrictions on use in children and adolescents due to respiratory adverse events

**Singapore**. The Health Sciences Authority (HSA) has worked with marketing authorization holders to update the package inserts of codeine-containing products to include the restriction of the use in children and adolescents.

Codeine is used for the treatment of pain and the relief of cough and cold. It is available in various dosage forms such as tablets, syrups and injections.

The HSA first issued an interim safety update in 2014 to health-care professionals which summarized the overseas recommendations on the use of codeine-containing products for pain relief in paediatric patients. It also informed health-care professionals that the HSA would be conducting a comprehensive review of such products in Singapore for pain relief and for the relief of cough symptoms in children. Subsequently, a Dear Health-care Professional Letter was issued in July 2016 regarding new restrictions on the use of codeine-containing products in order to reduce the risk of death and respiratory depression in infants and children.

To date, the HSA has received five reports of respiratory adverse events (AE) such as dyspnoea and bronchospasm in children between nine to 16-years of age associated with the use of codeine-containing cough products in Singapore. No deaths or cases of severe respiratory depression have been reported in Singapore.

Taking into consideration the current available scientific evidence, input from clinical experts in Singapore, local and international AE reports, the potential for serious and fatal AEs, Singapore population and international regulatory actions, the HSA has reviewed the benefits versus the risks of codeine and recommended the restrictions on the use of codeine-containing products in children and adolescents in Singapore. It is recommended that use is restricted in indications such as post-operative pain following surgical procedures, unproductive coughs, and caution is taken when used in children with underlying respiratory conditions.

***Reference:***
Product Safety Alerts, HSA, 20 December 2016 (*http://www.hsa.gov.sg/*)

*(See WHO Pharmaceuticals Newsletters No.6 and No.1 in 2016, No.4 and No.3 in 2015, No.5 and No.4 in 2013, and No.5 in 2012 for related information)*

## Combined hormonal contraceptives

### Risk of venous and arterial thromboembolism

**Australia**. The Therapeutic Goods Administration (TGA) has recommended that the Product Information and Consumer Medicine Information documents for combined hormonal contraceptives (CHCs) should be updated to ensure clearer and more consistent information is provided across products.

A review conducted by the TGA found that while the risk of venous thromboembolism (VTE), such as deep vein thrombosis and pulmonary embolism for women, is generally rare, the risk was slightly increased for women using combined hormonal contraceptives (CHCs).

The review also found that, based on currently available data, the increase in risk of VTE varied according to the progestogen included in the CHC. The risk of arterial

thromboembolism (ATE), such as myocardial infarction or stroke, is also increased with the use of CHCs, however, it is still very rare, and there is no evidence for differences in risk between CHCs.

The TGA has advised that health-care professionals should note the risk of venous thromboembolism is increased in women taking a combined hormonal contraceptive containing ethinyloestradiol and a progestogen and that, based on current data, the risk varies according to the progestogen used. The risk of arterial thromboembolism is also increased, however, there is currently no evidence that risk varies according to the progestogen used.

***Reference:***
Medicines Safety Update, TGA, Vol. 7, No. 5, October-December 2016 (*www.tga.gov.au*)

*(See WHO Pharmaceuticals Newsletters No.4 in 2015, No.6 and No.4 in 2013 for related information)*

## Direct-acting antivirals for hepatitis C treatment

### Potential risk of hepatitis B virus reactivation

**1. Canada**. Health Canada has recommended that the safety information for all direct-acting antivirals (DAAs) should be

sofosbuvir/velpatasvir (Epclusa®), asunaprevir (Sunvepra®) and elbasvir/grazoprevir (Zepatier®)) are prescription medicines used to treat chronic HCV infection in adult patients.

Health Canada carried out a safety review following reports of HBV reactivation in patients infected with both HBV and HCV treated with DAAs.

At the time of the review, Health Canada had not received any Canadian reports of HBV reactivation related to DAA use in patients infected with both HBV and HCV.

A total of 13 international reports of HBV reactivation were retrieved from different sources. Of these, 12 reports were considered to be possibly related to the use of DAAs: 11 reports reported the use of sofosbuvir or products with sofosbuvir and ledipasvir; one reported daclatasvir use. Of the 13 reports one could not be reviewed further because it did not provide enough information. Three of the 13 reports described symptoms of moderate HBV reactivation. One of the cases reported severe HBV reactivation resulting in liver failure and the patient needed a liver transplant.

Two studies of the use of DAAs in patients infected with both HCV and HBV reported an increase in viral genes (HBV DNA) in some of the patients. This could lead to reactivation

all patients for hepatitis B before starting treatment with DAAs; patients infected with both hepatitis B and C viruses must be monitored and managed according to current clinical guidelines. These measures aim to minimize the risk of hepatitis B reactivation with DAAs.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) carried out a review of DAAs. It looked into cases of returning signs and symptoms of previously inactive hepatitis B infection (re-activation) when patients were treated with DAAs for hepatitis C.

The PRAC recommendation to include a warning in the prescribing information about hepatitis B reactivation and how to minimize it, has now been endorsed by EMA's Committee for Medicinal Products for Human Use (CHMP).

In addition to data on hepatitis B reactivation, EMA also reviewed data suggesting that patients treated with DAAs who have previously been treated for liver cancer could be at risk of their cancer returning early. The CHMP agreed that companies should carry out a study to evaluate the risk of liver cancer returning with DAAs. In this context, further research is also needed on the risk of new liver cancers in patients with chronic hepatitis C and cirrhosis (liver scarring) that are treated with DAAs.