Drug News
藥物情報

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This is a monthly digest of local and overseas drug safety news released by the Drug Office of the Department of Health in February 2019 with relevant information update before publish. For the latest news and information, please refer to public announcements or the website of the Drug Office of the Department of Health (http://www.drugoffice.gov.hk).

Safety Update

EU: Suspension of fenspiride medicines due to potential risk of heart rhythm problems

On 15 February 2019, the European Medicines Agency (EMA) of the European Union (EU) announced that the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended an EU-wide suspension of fenspiride medicines, used in children and adults to relieve cough caused by lung diseases.

The suspension is a precautionary measure to protect patients while the PRAC reviews the risk of QT prolongation and torsades de pointes (abnormalities of the heart's electrical activity that may lead to heart rhythm disturbances).

Cases of heart rhythm problems had been reported in patients who had taken these medicines in the past. To explore the potential link between fenspiride and these heart rhythm problems, animal studies were carried out which now show that fenspiride has the potential to prolong QT in humans.

The PRAC will now examine all the available evidence and make recommendations on the action to be taken on marketing authorisations for fenspiride medicines across the EU. Once the review is concluded, the EMA will communicate further and provide updated guidance to patients and healthcare professionals.

Information for patients:
- Safety data indicate that cough medicines containing fenspiride could cause sudden serious heart rhythm problems.
- While authorities review all the evidence, patients are advised to stop taking these medicines.
- Patients are only at risk of heart rhythm problems with fenspiride while they are taking these medicines.
- If they are taking a cough medicine containing fenspiride, contact their doctor or pharmacist for advice on alternative treatments, if needed.
- If they have any concerns about the medicine, discuss them with their doctor or pharmacist.

Information for healthcare professionals:
- As a precaution and while the review is ongoing, healthcare professionals should advise their patients to stop taking fenspiride medicines.
- The provisional suspension of fenspiride medicines is based on recent nonclinical studies (hERG channel binding and *in vitro* animal model studies) that showed that fenspiride has the potential to increase QT intervals in humans. These data were supportive of a previously suspected link between fenspiride and QT prolongation/ torsades de pointes in humans, which was based on a limited number of case reports.
- Given the authorised use of fenspiride for symptomatic treatment only and the seriousness of QT prolongation, the medicines are provisionally suspended pending the results of an urgent EU safety review.
- Healthcare professionals will be informed in writing about the suspension, and further information will be provided as needed and once the review has concluded.

The review of fenspiride has been initiated at the request of France, and the review is being carried

out by the PRAC, the committee responsible for the evaluation of safety issues for human medicines. While the review is ongoing, the PRAC has recommended suspending the medicines to protect public health. Once the PRAC concludes its review, its recommendations will be forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a position.

In Hong Kong, there is one registered pharmaceutical product containing fenspiride, namely Fenspiride Tab 40mg "P.L." (HK- 59766). The above product is registered by Julius Chen & Co (HK) Ltd and it is classified as a non-poison. As of 5 March 2019, the Department of Health (DH) has not received any case of adverse drug reaction (ADR) related to fenspiride. In light of the above EMA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 18 February 2019. Since the EMA's review is ongoing, the DH will remain vigilant on the conclusion of the EMA review and any safety updates on fenspiride medicines issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

Canada: Opioid-containing cough and cold products - Assessing the potential risk of opioid use disorder and related harms in children and adolescents

On 18 February 2019, Health Canada announced that it reviewed the risk of opioid use disorder and related harms from cough and cold products containing opioids (including codeine, hydrocodone or normethadone) after the United States (US) Food and Drug Administration (FDA) advised against using these products in children and adolescents in 2018.

At the time of this review, Health Canada found limited information on reports of opioid use disorder among children and adolescents related to the use of opioid-containing cough medications from either Canadian or international reports. Like other opioids, codeine, hydrocodone, and normethadone may lead to opioid use disorder. However, it is often difficult to detect and recognize the signs and symptoms of opioid use disorder in children and adolescents, and these may go unreported. A review done by the Canadian Agency for Drugs and Technologies in Health found a lack of published evidence to support codeine use in children for cough and cold symptoms. Health Canada reviewed the published literature, which suggests that adolescents are at a greater risk of problematic opioid use and overdose, while younger children are at a greater risk of accidental poisoning. The scientific literature also suggests a possible link between exposure to opioid-containing products in adolescence and a higher risk of problematic opioid use later in life. National and provincial data indicate a concerning increase in opioid-related harms in children and adolescents.

Health Canada's safety review found limited evidence to link opioid-containing cough and cold products with opioid use disorders and related harms in children and adolescents. These products are linked to other known harms (i.e., breathing problems), and there is limited evidence to support the effectiveness of these products in children and adolescents. There are other products available in Canada to help relieve the symptoms of cough and cold in children.

Therefore, Health Canada, as a precautionary measure, is advising Canadians against the use of these products among children and adolescents under 18 years of age. Health Canada will notify the manufacturers to update the product safety information of opioid-containing cough and cold products to limit the recommended age of use (indication) to adults only, 18 years of age and older. Health Canada will also inform Canadians and healthcare professionals about these updates through an Information Update and a Health Product InfoWatch communication.

In Hong Kong, there are 333 registered pharmaceutical products containing codeine, which is an ingredient used to relieve cough. There is no registered pharmaceutical product containing hydrocodone or normethadone. As of 5 March 2019, the DH has received 4 cases of ADR related to codeine. News related to the limitation of the use of opioid-containing cough and cold medicines to adults (18 years of age and older) was previously issued by the US FDA and China National Medical

Products Administration (NMPA), and was reported in the Drug News Issue No. 99. The DH issued a letter to inform local healthcare professionals to draw their attention on 12 January 2018.

On 12 June 2018, the Registration Committee of the Pharmacy and Poisons Board (Registration Committee) discussed the matter, and decided to keep vigilant on any update from other health authorities. The DH will remain vigilant on safety update of the matter issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

UK: Carbimazole: increased risk of congenital malformations; strengthened advice on contraception

On 18 February 2019, the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (UK) announced that carbimazole is associated with an increased risk of congenital malformations when used during pregnancy, particularly in the first trimester of pregnancy and at high doses (15 mg or more of carbimazole daily). Carbimazole is a prodrug that undergoes rapid metabolism to the active metabolite, thiamazole. Thiamazole (synonym methimazole) is an antithyroid agent that acts by blocking the production of thyroid hormones. Thiamazole is not authorised for use in the UK.

Adequate treatment of hyperthyroidism in pregnant women prevents serious maternal and foetal complications. Carbimazole crosses the placental barrier and can cause foetal harm. An EU review of available evidence from epidemiological studies and case reports concluded there was evidence that carbimazole is associated with an increased risk of congenital malformations, especially when administered in the first trimester of pregnancy and at high doses (15 mg or more of carbimazole daily). Reported malformations include aplasia cutis congenita (absence of a portion of skin, often localised on the head), craniofacial malformations (choanal atresia; facial dysmorphism), defects of the abdominal wall and gastrointestinal tract (exomphalos, oesophageal atresia, omphalo-mesenteric duct anomaly), and ventricular septal defect.

The Patient Information Leaflet advises patients to tell their doctor straight away if they think they may be pregnant or are planning to have a baby. The use of carbimazole during pregnancy should be preserved for the situations in which a definitive therapy of the underlying disease (thyroidectomy or radioiodine treatment) was not suitable prior to pregnancy and in case of new occurrence or reoccurrence during pregnancy.

Healthcare professionals are advised:

- Carbimazole is associated with an increased risk of congenital malformations when used during pregnancy, particularly in the first trimester of pregnancy and at high doses (15 mg or more of carbimazole daily).
- Women of childbearing potential should use effective contraception during treatment with carbimazole.
- Carbimazole should only be considered in pregnancy after a thorough individual assessment of benefits and risks of treatment, and only at the lowest effective dose without additional administration of thyroid hormones; close maternal, foetal, and neonatal monitoring is recommended.

In Hong Kong, there are 6 registered pharmaceutical products containing carbimazole, and 2 products containing methimazole. All products are prescription-only medicines. As of 5 March 2019, the DH has received one case of ADR related to carbimazole, but this case is not related to congenital malformations. The DH has not received any case of ADR related to methimazole. Congenital defects of carbimazole and methimazole have already been documented in overseas reputable drug references such as the "Martindale: The Complete Drug Reference". The DH will remain vigilant on safety update of the drugs issued by other overseas drug regulatory authorities.

UK: Carbimazole: risk of acute pancreatitis

On 18 February 2019, the MHRA announced that cases of acute pancreatitis have been reported very infrequently during treatment with carbimazole. Carbimazole is a prodrug that undergoes rapid metabolism to the active metabolite, thiamazole. Thiamazole (synonym methimazole) is an

antithyroid agent that acts by blocking the production of thyroid hormones. Thiamazole is not authorised for use in the UK.

An EU review has found post-marketing reports of acute pancreatitis associated with the use of products containing carbimazole and thiamazole. In the UK, no Yellow Card reports of acute pancreatitis associated with carbimazole treatment have been received over a period of 55 years; however, a small number of reports have been received in other countries. Although the mechanism for development of acute pancreatitis is poorly understood, the presence of cases reporting recurrent acute pancreatitis with a decreased time to onset after re-exposure to carbimazole suggests a possible immunological mechanism.

The product information for products containing carbimazole is being updated to include risk of acute pancreatitis.

Healthcare professionals are advised:

- Cases of acute pancreatitis have been reported very infrequently during treatment with carbimazole.
- If acute pancreatitis occurs, stop carbimazole treatment immediately.
- Do not use carbimazole in patients with a history of acute pancreatitis in association with previous treatment.
- Re-exposure may result in life-threatening acute pancreatitis with a decreased time to onset.
- Carbimazole must be immediately discontinued in patients who develop acute pancreatitis during treatment. Patients should be switched to an alternative therapy on the basis of an assessment of the individual benefits and risks.

In Hong Kong, there are 6 registered pharmaceutical products containing carbimazole, and 2 products containing methimazole. All products are prescription-only medicines. As of 5 March 2019, the DH has received one case of ADR related to carbimazole, but this case is not related to acute pancreatitis. The DH has not received any case of ADR related to methimazole. In light of the above MHRA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 19 February 2019, and the matter will be discussed by the Registration Committee.

US: FDA adds Boxed Warning for increased risk of death with gout medicine Uloric (febuxostat)

On 21 February 2019, the US FDA announced that it has concluded there is an increased risk of death with Uloric (febuxostat) compared to another gout medicine, allopurinol. This conclusion is based on FDA in-depth review of results from a safety clinical trial that found an increased risk of heart-related death and death from all causes with Uloric.

As a result, the FDA is updating the Uloric prescribing information to require a Boxed Warning, the FDA's most prominent warning, and a new patient Medication Guide. The FDA is also limiting the approved use of Uloric to certain patients who are not treated effectively or experience severe side effects with allopurinol.

Patients should tell their healthcare professional if they have a history of heart problems or stroke and discuss the benefits and risks of using Uloric to treat their gout. They should seek emergency medical attention right away if they experience the following symptoms while taking Uloric: chest pain, shortness of breath, rapid or irregular heartbeat, numbness or weakness on one side of their body, dizziness, trouble talking, sudden severe headache. They should not stop taking Uloric without first talking to their healthcare professional, as doing so can worsen their gout.

Healthcare professionals should reserve Uloric for use only in patients who have failed or do not tolerate allopurinol. They should counsel patients about the cardiovascular risk with Uloric and advise patients to seek medical attention immediately if the patients experience the symptoms listed above.

When the FDA approved Uloric in 2009, the FDA included a Warning and Precaution regarding possible cardiovascular events in patients treated with Uloric in the current prescribing information and required the drug manufacturer, Takeda

Pharmaceuticals, to conduct a large postmarket safety clinical trial. The trial was conducted in more than 6,000 patients with gout treated with either Uloric or allopurinol. The primary outcome was a combination of heart-related death, non-deadly heart attack, non-deadly stroke, and a condition of inadequate blood supply to the heart requiring intervention, called unstable angina. The results showed that overall, Uloric did not increase the risk of these combined events compared to allopurinol. However, when the outcomes were evaluated separately, Uloric showed an increased risk of heart-related deaths and death from all causes. In patients treated with Uloric, 15 deaths from heart-related causes were observed for every 1,000 patients treated for a year compared to 11 deaths from heart-related causes per 1,000 patients treated with allopurinol for a year. In addition, there were 26 deaths from any cause per 1,000 patients treated for a year with Uloric compared to 22 deaths per 1,000 patients treated for a year with allopurinol. This safety trial was also discussed at a public Advisory Committee meeting of outside experts on 11 January 2019.

In Hong Kong, there are 2 registered pharmaceutical products containing febuxostat, namely Feburic Tablets 80mg (HK-61185) and Feburic Tablets 120mg (HK-61186) registered by Astellas Pharma Hong Kong Company Limited. Both products are prescription-only medicines. As of 5 March 2019, the DH has received one case of ADR related to febuxostat, but this case is not related to death. Related news was previously issued by the FDA, and was reported in the Drug News Issue No. 97. In light of the above FDA's updated safety information and recommendations, the DH issued a letter to inform local healthcare professionals to draw their attention on 22 February 2019 and the matter will be discussed by the Registration Committee.

Singapore: Tecentriq® (atezolizumab): A new important identified risk of immune-related myositis

On 22 February 2019, the Health Sciences Authority (HSA) of Singapore announced that Roche Singapore Pte Ltd would like to inform healthcare professionals of the new safety concern of immune-related myositis associated with Tecentriq® (atezolizumab). Dermatomyositis and polymyositis are amongst the most common types of myositis.

Diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine-kinase increase), and imaging (electromyography/magnetic resonance imaging) features, and is confirmed with a muscle biopsy. Healthcare professionals are advised to withhold Tecentriq® for moderate or severe (Grade 2 or 3) immune-related myositis and permanently discontinue the drug for recurrent severe or life-threatening myositis (recurrent Grade 3 and Grade 4). It is also recommended to administer corticosteroids and/or additional immunosuppressive agents for > Grade 2 events or if event does not improve after initial corticosteroids.

Roche Singapore Pte Ltd is working with the HSA to update the Singapore package insert for Tecentriq® to include the risk of immune-related myositis.

In Hong Kong, Tecentriq Concentrate for Solution for Infusion 1200mg/20ml (HK-65567) is a registered pharmaceutical product containing atezolizumab. The product is registered by Roche Hong Kong Limited, and is a prescription-only medicine. As of 5 March 2019, the DH has received 24 cases of ADR related to atezolizumab, but these cases are not related to myositis. In light of the above HSA's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 26 February 2019. The DH will remain vigilant on safety update issued by other overseas drug regulatory authorities for consideration of any action deemed necessary.

Canada: Ferriprox (deferiprone) - Assessing the potential risk of brain and nervous system (neurological) disorders in children

On 25 February 2019, Health Canada announced that it reviewed the potential risk of neurological disorders such as difficulty walking or difficulty with the coordination of movement in children when Ferriprox is used at recommended doses.

This safety review was triggered after 2 reports were published suggesting this risk in children taking Ferriprox. At the time of the review, the product safety information for Ferriprox in Canada included a warning to inform that similar neurological disorders have been observed in 2 children treated with 2.5 times the recommended doses of Ferriprox.

At the time of the review, Health Canada had not received any Canadian reports of neurological disorders linked to the use of Ferriprox in children. Health Canada's safety review found 2 international case reports of neurological disorders in children that were treated with Ferriprox at recommended doses. In one report, there was a link between neurological disorders and the use of Ferriprox. In the other report, the link between neurological disorders and the use of Ferriprox was possible, but there were other factors (such as, the treatment condition, and other neurological/medical conditions) that may have also caused the neurological disorders.

Health Canada's review concluded that there may be a link between Ferriprox and neurological disorders in children when it is used at recommended doses, and not only at higher doses as currently referenced in the product safety information. Health Canada will notify the manufacturer to update the current warnings in the safety information to reflect that cases of neurological disorders in children have also been observed at recommended doses of Ferriprox.

In Hong Kong, there are 3 registered pharmaceutical products containing deferiprone, namely Ferriprox Tab 500mg (HK-49758), Ferriprox Oral Solution 100mg/ml (HK-58937) and Ferriprox Film-coated Tablets 1000mg (HK-62074). These products are registered by Hind Wing Co Ltd (Hind Wing), and are prescription-only medicines. As of 5 March 2019, the DH has not received any case of ADR related to deferiprone. In September 2018, Hind Wing submitted application for change of product insert to include neurological disorders in children with standard doses of deferiprone. The DH is working with the company to update the safety information of the products. In light of the above Health Canada's announcement, the DH issued a letter to inform local healthcare professionals to draw their attention on 26 February 2019. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

US: Safety trial finds risk of blood clots in the lungs and death with higher dose of tofacitinib (Xeljanz, Xeljanz XR) in rheumatoid arthritis patients; FDA to investigate

On 25 February 2019, the US FDA announced that a safety clinical trial found an increased risk of blood clots in the lungs and death when a 10 mg twice daily dose of tofacitinib (Xeljanz, Xeljanz XR) was used in patients with rheumatoid arthritis (RA). The FDA has not approved this 10 mg twice daily dose for RA; this dose is only approved in the dosing regimen for patients with ulcerative colitis.

In this ongoing safety trial required by the FDA when it approved tofacitinib for RA, the drug manufacturer, Pfizer, is transitioning patients who were on the high 10 mg twice daily dose to the lower, currently approved dose of 5 mg twice daily. This trial will continue and is expected to be completed by the end of 2019. The FDA is working with the manufacturer to evaluate other currently available safety information for tofacitinib and will update the public with any new information based on the ongoing review.

Healthcare professionals should follow the recommendations in the tofacitinib prescribing information for the specific condition they are treating. Monitor patients for the signs and symptoms of pulmonary embolism, and advise them to seek medical attention immediately if they experience them.

Patients should not stop or change their dose of tofacitinib without first talking to their healthcare professional, as doing so may worsen their condition. Patients taking tofacitinib should seek medical attention immediately if they experience symptoms of a blood clot in their lungs or other unusual symptoms such as sudden shortness of breath or difficulty breathing, chest pain or pain in their back, coughing up blood, excessive sweating, clammy or bluish coloured skin.

When the FDA first approved tofacitinib, it required a clinical trial among patients with RA to evaluate the risk of heart-related events, cancer, and opportunistic infections with the medicine at two doses (10 mg twice daily and 5 mg twice daily) in combination with methotrexate in comparison to another drug called a tumor necrosis factor (TNF) inhibitor. RA patients in the trial were required to be at least 50 years old and have at least one cardiovascular risk factor. During the most recent analysis of the trial, an external data safety monitoring committee found an increased occurrence of blood clots in the lungs and death in patients treated with tofacitinib 10 mg twice daily compared to patients treated with tofacitinib 5 mg twice daily or a TNF inhibitor.

In Hong Kong, Xeljanz Tablets 5mg (HK-63303) is a registered pharmaceutical product containing tofacitinib. The product is registered by Pfizer Corporation Hong Kong Limited, and is a prescription-only medicine. As of 5 March 2019, the DH has received 3 cases of ADR related to tofacitinib, but these cases are not related to blood clots in the lungs. As the safety trial is ongoing, the DH will remain vigilant on the results of the trial and safety update issued by the FDA and other overseas drug regulatory authorities for consideration of any action deemed necessary.

Canada: Proscar and Propecia (finasteride) - Assessing the potential risk of suicidal thoughts and/or behaviour (suicidal ideation)

On 26 February 2019, Health Canada announced that it reviewed the potential risk of suicidal ideation with use of Proscar or Propecia (finasteride) due to reported cases of suicidal ideation and self-injury received in Canada and internationally. The cases led to the investigation of the possible relationship between finasteride use and suicidal ideation through a number of assessments.

The topic of finasteride and suicide/self-injury has been monitored on an ongoing basis by Health Canada since 2011. A first safety review was completed in 2012, and it was recommended that the topic be re-assessed in 2 years. A second safety review was completed in 2014, where the information at that time could not confirm if there was a link or not between finasteride use and suicide/self-injury. It was recommended as a precautionary measure to inform physicians of the potential risk and assess the topic again after another 2 years. As a result of this recommendation and reported cases, Health Canada began this safety review.

At the time of the review, Health Canada had received 26 Canadian reports of events related to suicide or self-injury with the use of finasteride. Between 2012 and 2016, the Canadian reporting rate for finasteride and suicide/self-injury-related events increased by 2.5 times. In the assessment of the Canadian reports, a cause and effect relationship could not be confirmed or denied, and as a result, a link between finasteride and suicide/self-injury-related events was deemed possible. A search in the World Health Organization's Adverse Drug Reaction Database found 368 international reports of suicide/self-injury-related events reported in patients treated with finasteride, up to 16 September 2018. There were 5 studies reviewed that were published between 2015-2018 on finasteride and suicide-related events. These publications support a link between finasteride use and the risk of suicidal ideation. The international reports, literature, and regulatory information that were reviewed could neither confirm nor deny a cause and effect relationship between finasteride and suicide/self-injury.

Health Canada's review concluded that there may be a link between Proscar and Propecia (finasteride) and the risk of suicidal ideation. Health Canada has notified the manufacturer to update the Canadian product information to include a warning on this potential safety issue.

In Hong Kong, there are 38 registered pharmaceutical products containing finasteride, and all products are prescription-only medicines. As of 5 March 2019, the DH has received one case of ADR related to finasteride, but this case is not related to suicidal ideation. Related news was previously issued by the MHRA, and was reported in the Drug News Issue No. 91. The DH issued a letter to inform local healthcare professionals to draw their attention on 25 May 2017. In September 2017, the Registration Committee discussed the matter, and decided that the sales pack labels and/or

package inserts of finasteride-containing products should include warnings on suicidal ideation. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

US: Camber Pharmaceuticals, Inc. issues voluntary nationwide recall of Losartan Potassium Tablets, USP, 25 mg, 50 mg and 100 mg due to the detection of trace amounts of *N*-nitroso *N*-methyl 4-amino butyric acid (NMBA) impurity found in the active pharmaceutical ingredient (API)

On 28 February 2019, the US FDA announced that Camber Pharmaceuticals, Inc. was recalling 87 lots of Losartan Tablets USP 25 mg, 50 mg, and 100 mg to consumer level. This recall was prompted due to the detection of trace amounts of NMBA, a possible process impurity or contaminant in an API, manufactured by Hetero Labs Limited, Unit – I (API manufacturer).

NMBA is a potential human carcinogen. As of 28 February 2019, Camber has not received any reports of adverse events related to this recall.

The affected Losartan includes 87 lot numbers which are listed below:

Losartan Potassium Tablets USP 25 mg

NDC Number	Tablets per Bottle	Lot Number	Expiry
31722-700-90	90	LOP17026B, LOP17050, LOP17051, LOP17052, LOP17053	Sep-19
		LOP17061	Oct-19
		LOP18035, LOP18036	Dec-19
31722-700-05	500	LOP17026	Sep-19
31722-700-10	1000	LOP17006	May-19
		LOP17025	Sep-19
		LOP17068	Oct-19
		LOP18037, LOP18038, LOP18039	Dec-19
		LOP18057	Jan-20

Losartan Potassium Tablets USP 50mg

NDC Number	Tablets per Bottle	Lot Number	Expiry
31722-701-30	30	LOP17028C	Sep-19
		LOP17064A	Nov-19
31722-701-90	90	LOP17027	Sep-19
		LOP17063, LOP17093	Nov-19
		LOP17094, LOP17095, LOP17097A, LOP17105, LOP17107	Dec-19
31722-701-10	1000	LOP17004	Dec-19
		LOP17028B	Sep-19
		LOP17048, LOP17049	Oct-19
		LOP17056, LOP17073, LOP17074, LOP17076	Nov-19
		LOP17096	Dec-19
		LOP18077A, LOP18078, LOP18079, LOP18080	Feb-20
		LOP18081, LOP18084, LOP18095, LOP18096	Mar-20

Losartan Potassium Tablets USP 100 mg

NDC Number	Tablets per Bottle	Lot Number	Expiry
31722-702-30	30	LOP17011	Aug-19
		LOP17087	Nov-19
31722-702-90	90	LOP17012, LOP17013	Aug-19
		LOP17042, LOP17043	Oct-19
		LOP17044, LOP17045	Nov-19
		LOP18024, LOP18025, LOP18026, LOP18027, LOP18028, LOP18029, LOP18030	Dec-19
31722-702-10	1000	LOP17005	May-19
		LOP17014	Aug-19
		LOP17016, LOP17023	Sep-19
		LOP17083	Oct-19
		LOP17084, LOP17085, LOP17086	Nov-19
		LOP18021, LOP18022, LOP18023, LOP18031, LOP18032, LOP18033, LOP18050, LOP18051	Dec-19
		LOP18109, LOP18111	Mar-20
		LOP18122, LOP18123, LOP18124, LOP18125, LOP18126, LOP18127, LOP18128, LOP18129, LOP18130, LOP18131C, LOP18133	Jun-20

In Hong Kong, as of 5 March 2019, there are 250 registered pharmaceutical products containing valsartan (83 products), candesartan (19 products),

irbesartan (62 products), losartan (69 products) and olmesartan (17 products). All products are prescription-only medicines.

Regarding impurities in valsartan, a public announcement was issued on 6 July 2018, and the DH issued letters to inform local healthcare professionals on 6 July 2018, 9 July 2018, 25 July 2018 and 3 August 2018. Related news for the detection of impurities in sartan-containing products was also previously issued by various overseas drug regulatory authorities, and was reported in the Drug News Issue No. 105, 106, 107, 108, 109, 110 and 111.

In brief, there are four manufacturers, namely Zhejiang Huahai, Zhejiang Tianyu and Zhuhai Rundu in China and Hetero Labs Limited in India, reported to have detection of trace amounts of *N*-nitrosodimethylamine (NDMA) in the valsartan API by various overseas drug regulatory authorities. The DH contacted the certificate holders of all registered valsartan products to follow up on the local impact regarding valsartan API produced by the above mentioned manufacturers.

For API produced by Zhejiang Huahai, there are 5 affected products (HK-61786, HK-61787, HK-61784, HK-61785 and HK-60794) marketed in Hong Kong. The DH instructed the certificate holders to recall all the products from the market as a precautionary measure on 6 July 2018, and the DH noted that all the recalls have been completed.

For API produced by Zhejiang Tianyu, amongst the registered pharmaceutical products containing valsartan, there is only one product namely Retoni Tablets 80mg (HK-65604) registered by Swiss Pharmaceutical Co Limited (Swiss Pharmaceutical) which has used API produced by Zhejiang Tianyu and is available in the local market. As confirmed with Swiss Pharmaceutical, the API was tested by the Taiwan Food and Drug Administration (TFDA) and the company has not received any notice from the TFDA for NDMA contamination. The DH collected samples of Retoni tablets for analysis and no NDMA was detected.

For API produced by Zhuhai Rundu and Hetero Labs Limited, the certificate holders confirmed that the valsartan products available in local market are not manufactured using API produced by Zhuhai Rundu or Hetero Labs Limited.

Regarding the announcements issued by various overseas drug regulatory authorities on the detection of the second impurity of *N*-nitrosodiethylamine (NDEA) in the valsartan API produced by Zhejiang Huahai, there should be no local impact as all valsartan products manufactured using API produced by Zhejiang Huahai have been recalled from the market.

Regarding the announcements issued by various overseas drug regulatory authorities on the detection of NDEA in the valsartan API produced by Mylan Laboratories Limited in India, the certificate holders confirmed that the valsartan products available in local market are not manufactured using API produced by this company.

Regarding the announcements issued by various overseas drug regulatory authorities on the detection of NDEA in the losartan API produced by Hetero Labs Limited, Zhejiang Huahai and IPCA in India, and the announcements on NDEA in the irbesartan API produced by Aurobindo Pharma in India and Zhejiang Huahai, the DH has contacted the certificate holders of all registered candesartan, irbesartan, losartan and olmesartan products and will continue to follow up on the impact of NDEA impurities on the products available in the local market. On 20 December 2018, the DH endorsed Actavis Hong Kong Limited to recall one batch (batch number: 058818) of Irbesartan HCT Actavis Tablets 150/12.5mg (HK-63378) from the market as a precautionary measure because an impurity was detected in one of the raw materials of this batch of product, a public announcement was issued on 20 December 2018 and is reported in Drug News Issue No 110. The DH noted that the recall has been completed.

As of 5 March 2019, the DH has received 16 cases of ADR related to valsartan, candesartan, irbesartan, losartan and olmesartan. None of them is concluded to be related to the presence of impurities such as NDMA, NDEA and/or NMBA. The DH has provided update information at Drug Office's website (www.drugoffice.gov.hk) and will

keep vigilant on any safety updates on detection of impurities in sartan-containing products issued by overseas regulatory authorities.

Patients who are taking the above products should not stop taking the medicines, but should seek advice from their healthcare professionals as soon as possible for proper arrangement.

Canada: Gilenya (fingolimod) - Assessing the potential risk of worsening multiple sclerosis symptoms after product withdrawal (rebound effect)

On 28 February 2019, Health Canada announced that it reviewed the potential risk of worsening multiple sclerosis (MS) symptoms (rebound effect) after Gilenya withdrawal. The safety review was triggered by reports of severe MS symptoms following the withdrawal of Gilenya. Severe worsening of MS symptoms were mostly reported within 12 weeks (with rare cases reported up to 24 weeks) following withdrawal of Gilenya.

At the time of the review, Health Canada identified 29 international reports of severe worsening of MS disease progression after Gilenya withdrawal. Most patients (27/29) required treatment for the symptoms they experienced and, at the time of reporting, the majority of patients partially recovered following treatment with other agents (18/27). Twelve of these 29 patients required hospitalization. This safety review also looked at information from the manufacturer and the scientific literature about the risk of rebound effect after Gilenya withdrawal. The information from the manufacturer and the scientific literature supported the potential risk of worsening MS symptoms after Gilenya withdrawal.

Product information for Gilenya in Canada includes information about the risk of worsening MS symptoms after Gilenya withdrawal. It also recommends monitoring patients for development of severe worsening of MS symptoms after withdrawal of Gilenya and beginning appropriate treatment as needed. This information can be found in the Warnings and Precautions section of the product information for Gilenya.

Health Canada's safety review concluded that there may be a link between the withdrawal of Gilenya and the worsening of MS symptoms. The product safety information for Gilenya has been updated to inform Canadians and healthcare professionals about this potential safety issue.

In Hong Kong, Gilenya Hard Capsules 0.5mg (HK-61192) is a pharmaceutical product registered by Novartis Pharmaceuticals (HK) Limited, and is a prescription-only medicine. As of 5 March 2019, the DH has received 3 cases of ADR related to fingolimod, but these cases are not related to worsening of multiple sclerosis after stopping the drug. Related news was previously issued by the US FDA, and was reported in the Drug News Issue No. 109. The DH issued a letter to inform local healthcare professionals to draw their attention on 21 November 2018. In February 2019, the Registration Committee discussed the matter, and decided that the sales pack or package insert of the product should include the safety information on severe worsening of multiple sclerosis after stopping the drug. The DH will remain vigilant on safety update of the drug issued by other overseas drug regulatory authorities.

A product containing any western drug ingredient must be registered under the Pharmacy and Poisons Ordinance before it can be sold in Hong Kong. Part 1 poisons should be sold at registered pharmacies under the supervision of registered pharmacists. Illegal sale or possession of Part 1 poisons and unregistered pharmaceutical products are offences under the Pharmacy and Poisons Ordinance (Cap. 138). The maximum penalty is a fine of $100,000 and two years' imprisonment for each offence. Antibiotics can only be supplied at registered pharmacies by registered pharmacists or under their supervision and upon a doctor's prescription. They should only be used under the advice of a doctor. Illegal sale or possession of antibiotics are offences under the Antibiotics Ordinance (Cap. 137) and the maximum penalty is a $30,000 fine and one year's imprisonment for each offence.

Under the Import and Export Ordinance (Cap. 60), pharmaceutical products must be imported or exported under and in accordnance with an import or export licence issued under the Import and Export Ordinance. Illegal import or export of pharmaceutical products are offences under the Import and Export Ordinance (Cap. 60) and the maximum penalty is a fine of $500,000 and 2 years' imprisonment.

Update on Drug Office's website: You can now search the newly registered medicines in the past year at http://www.drugoffice.gov.hk/eps/drug/newsNRM60/en/healthcare_providers?pageNoRequested=1.
Details of ALL registered pharmaceutical products can still be found in the Drug Office website at http://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/news_informations/reListRPP_index.html.

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The purpose of Drug News is to provide healthcare professionals with a summary of local and overseas drug safety news released. Healthcare professionals are advised to keep update with the information and provide corresponding advice or therapeutic measure to patients and public.