Safety news

Safety warnings

Edoxaban:
Interstitial lung disease
Japan – The PMDA has informed health professionals that cases of interstitial pneumonia have been observed in patients treated with the anti-clotting agent edoxaban (Lixiana*) in Japan. Based on the PMDA’s investigation the MHLW has recommended updates to the product information of this medicine. Patients should be carefully monitored. If signs and symptoms such as cough, shortness of breath, dyspnoea, fever or abnormal chest sound are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be done immediately. If interstitial lung disease is suspected, administration of edoxaban should be discontinued and appropriate measures such as administration of corticosteroid taken.

► PMDA Summary of investigation results and MHLW Revision of precautions, 11 January 2018.

Teriparatide:
Shock and loss of consciousness
Japan – Following reported cases of loss of consciousness and acute hypotension in patients treated with the osteoporosis medicine teriparatide in Japan, leading to cardiac arrest and/or respiratory arrest in some cases, the PMDA has recommended that clearer warnings should be added to the product information about the risk of seizures, shock and loss of consciousness associated with the use of teriparatide. These events may occur immediately or up to several hours after administration. In some patients the onset was after several months of treatment.(1)

An overview of the risks of teriparatide—including hypercalcaemia, a range of side effects due to dilatation of vessels, and osteosarcoma reported in animal toxicity studies and leading to suspension of initial clinical trials—has been published in the independent drug bulletin of the Japan Institute of Pharmacovigilance. The authors conclude that the benefit/risk balance is negative in the treatment of osteoporosis.(2)

► (1) PMDA Summary of investigation results and MHLW Revision of precautions (teriparatide acetate, teriparatide genetical recombination), 11 January 2018.


Clarithromycin:
Risk of cardiovascular events
United States of America – The FDA has advised caution in the use of the antibiotic clarithromycin in patients with heart disease, even for short periods. Clarithromycin is associated with a potential increased risk of heart problems or death that can occur years later. This safety issue was first observed in a large clinical trial, and was confirmed in a 10-year follow-up study in patients with coronary heart disease.

Health care professionals should weigh the benefits and risks of clarithromycin and consider prescribing other antibiotics in patients with heart disease. If such patients are given clarithromycin they should be alerted to the risks and advised to seek medical care immediately if they experience
any signs and symptoms of a cardiovascular problems such as a heart attack or stroke. The product information has been updated.
►FDA Drug safety communication, 22 February 2018.

Atezolizumab:
Myocarditis
Canada – The marketing authorization holder, in agreement with Health Canada, has informed health professionals that severe cases of myocarditis have been reported in patients treated with the anti-cancer medicine ateziolizumab (Tecentriq®) in clinical trials. Healthcare professionals should monitor patients on ateziolizumab for signs and symptoms of myocarditis. Treatment should be withheld in patients with Grade 2 myocarditis, and permanently discontinued in patients with Grade 3 or 4 myocarditis. Patients on ateziolizumab who develop myocarditis should receive corticosteroids and/or additional immunosuppressive agents as clinically indicated.

The Canadian product information has been updated to include this new safety information.
►Health Canada Advisory, 14 February 2018.

Lenvatinib:
Gallbladder inflammation
Japan – The PMDA has informed health professionals that cases of acute cholecystitis have been reported in patients treated with the anti-cancer medicine lenvatinib mesilate (Lenvima®) in Japan and in other countries. Two of the cases observed in Japan had a fatal outcome. A warning has been added to the product information, recommending that patient should be monitored and appropriate measures taken —such as stopping the medicine—if any abnormalities are observed.
►PMDA Summary of investigation results and MHLW Revision of precautions, 11 January 2018.

Iomeprol, iohexol:
Severe skin reactions
Japan – Following reports of acute generalized exanthematous pustulosis (AGEP) in patients treated with the iodinated contrast media iomeprol and iohexol, the PMDA has recommended updates to the product information to warn about this potential adverse effect.
►PMDA Summary of investigation results, 13 February 2018.

Saccharomyces boulardii probiotics:
Do not use in critically ill or immunocompromised patients
Estonia – The marketing authorization holder, in agreement with the regulatory authority of Estonia, has informed health professionals that Saccharomyces boulardii-containing probiotic products should not be used in critically ill or immunocompromised patients, as they can cause fungaemia in very rare cases. Also, special care should be taken when handling of S. boulardii medicinal products in the presence of patients mainly with central venous catheters, but also with peripheral catheters, in order to avoid any contamination by touch and the spread of microorganisms by air. The product information has been updated to include these warnings.(1)

S. boulardii is a replacement for intestinal flora. It is used for adjuvant symptomatic treatment of diarrhoea as well as for prophylaxis and treatment of antibiotic-associated diarrhoea and recurrence of Clostridium difficile disease in addition to vancomycin and metronidazole. The update follows a review and recommendation by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC).(2)
►(1)Ravimiamet (Estonian medicines agency). Safety announcement, 13 February 2018. (Estonian)
(2)PRAC meeting minutes, September 2017.
Artemisia annua soft gel capsules: Reports of liver damage
New Zealand – Medsafe has alerted consumers that Artemisia annua extract may pose a risk of harm to the liver. A. annua extract is marketed in New Zealand as a natural dietary supplement for maintaining and supporting joint health and mobility. The warning follows reports of liver toxicity received by the Agency’s Centre for Adverse Reactions Monitoring (CARM). All the reports involved patients taking a specific product presented as soft gel capsules. Since the chemical composition of the A. annua extract in that product was not disclosed it is not clear if other products containing A. annua extract could have similar effects.
► Medsafe Alert communication, 15 February 2018.

Mitragyna speciosa (kratom): Opioid-like substance to be recalled in the U.S.
United States of America – The FDA has received numerous reports of adverse events associated with the use of food supplement products containing kratom (Mitragyna speciosa), including 44 reported deaths. Such products are not authorized in the U.S. The FDA has encouraged companies supplying kratom-containing products to organize a destruction and recall, and to submit data for evaluation of the products through the applicable regulatory pathway. Kratom is a plant that grows in Thailand, Malaysia, Indonesia and Papua New Guinea. The FDA has reviewed data suggesting that compounds in kratom share structural similarities with controlled opioid analgesics and have significant risks of abuse and adverse effects.
In addition the FDA and the U.S. Centers for Disease Control and Prevention (CDC) are monitoring a nationwide outbreak of a rare type of salmonella associated with kratom-containing capsules, teas and powders. This underscores the risk that unapproved products, which are not subject to manufacturing controls, may be contaminated with harmful bacteria.

To be withdrawn from the market

Hydroxyethyl starch: Earlier restrictions not sufficient
European Union – The EMA has endorsed the recommendation by its Pharmacovigilance Risk Assessment Committee (PRAC) to suspend the marketing authorizations for hydroxyethyl-starch solutions for infusion across the EU. These solutions are used as plasma volume replacement following acute blood loss to treat hypovolaemia in case cristalloids are not sufficient to stabilize the patient.
Restrictions had been introduced in the EU in 2013 to reduce the risks of these products for critically ill patients and those with sepsis and kidney injury. The PRAC has reviewed the results of two drug utilization studies together with other available data and feedback from stakeholders and experts, and has concluded that the earlier restrictions have not been sufficiently effective.

Daclizumab: Cases of inflammatory brain disorders
European Union – The EMA has recommended the immediate suspension and recall of the multiple sclerosis medicine daclizumab (Zinbryta®). This follows 12 cases of serious inflammatory brain disorders worldwide, including encephalitis and meningoencephalitis. Three of the
cases were fatal. The company that markets the medicine has voluntarily requested the withdrawal of the marketing authorization and has informed EMA of its decision to stop ongoing clinical studies.

No new patients should start treatment with daclizumab. Healthcare professionals should immediately contact patients on daclizumab and should stop their treatment and consider alternatives. Patients stopping treatment must be followed up for at least 6 months. (1)

In November 2017 the EMA had tightened its restrictions on the use of daclizumab introduced in July 2017 because of the risk of serious liver damage. (2) Available evidence also indicates that daclizumab could be linked to other immune-mediated disorders, such as blood dyscrasias, thyroiditis or glomerulonephritis. An urgent review is under way (see page 26).

► (1) EMA Press release, 7 March 2017.
► (2) WHO Drug Information, Issues 3 and 4 of 2017.

**Flupirtine:**
**Serious liver problems**

European Union – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the marketing authorization for the analgesic flupirtine be withdrawn. Following an earlier review, restrictions had been introduced in 2013 to limit the use of flupirtine to no more than two weeks in patients with acute pain who could not use other analgesics, subject to weekly liver function tests. These recommendations have not been sufficiently followed in clinical practice, and the PRAC could not identify any further measures that would adequately reduce the risk of liver problems associated with the use of flupirtine.


**Known risks**

**Obeticholic acid:**
**Liver decompensation or failure in incorrectly dosed patients**

United States of America – In an update to its communication of September 2017, the FDA has added its most prominent “Boxed Warning” and other updates to the product information for obeticholic acid (Ocaliva*) to clarify the recommendations for screening, dosing and monitoring based on the patient’s Child-Pugh score of liver impairment and any prior decompensation event. Obeticholic acid is used for the treatment of primary biliary cholangitis (PBC), a rare chronic liver disease. It has been incorrectly dosed daily instead of weekly in patients with moderate to severe PBC, increasing the risk of serious liver injury. The FDA is also requiring a medication guide for patients.

► FDA Drug Safety communication, 2 February 2018.

**Loperamide:**
**Packaging changes for safe use**

United States of America – Despite earlier warnings, the FDA continues to receive reports about serious heart problems occurring with excessive doses of the antidiarrhoeal medicine loperamide. Most cases are linked to abuse or misuse of loperamide, for example to increase its euphoric effects by combining it with other drugs, or to treat symptoms of opioid withdrawal. The maximum daily dose of loperamide for adults approved in the U.S. is 8 mg per day for over-the-counter use and 16 mg per day for prescription use. The FDA is working with manufacturers to use blister packs or other single dose packaging and to limit the number of doses in a package.

Retinoid-containing medicines: Updated measures to avoid use in pregnancy, neuropsychiatric disorders

European Union – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has recommended updated measures to avoid the use of retinoids in pregnancy as they can have harmful effects on the unborn child, and to warn about the possible risk of neuropsychiatric disorders.

The recommended pregnancy prevention measures depend on the type of retinoid. Oral medicines containing acitretin, alitretinoin or isotretinoin must be used in line with an updated pregnancy prevention programme, and the marketing authorization holders will conduct a study and a survey to assess the effectiveness of the new measures. For oral bexarotene and tretinoin, which are used under strict medical supervision to treat certain cancers, the current pregnancy prevention measures are considered appropriate. For topical retinoids the PRAC adopted a precautionary approach: Although their absorption is very low it could be increased by excessive use or skin lesions, and their use is not recommended in pregnancy or in women planning to have a baby.

A warning about the risk of neuropsychiatric disorders, such as depression, anxiety and mood changes, will be added to the prescribing information of oral retinoids. These events may be due to the medicine as well as the nature of the disease itself. No additional warning was considered necessary for topical retinoids.

Efavirenz: QT interval prolongation

Japan – The PMDA has informed health professionals about the outcomes of a clinical study, which has found that an increased blood concentration of efavirenz was associated with prolongation of the QT interval. The product information for efavirenz has been updated.

The product information approved in the EU and the U.S. states that QTc prolongation has been observed with efavirenz, and that alternatives to efavirenz should be considered in patients taking other medicine with a known risk of Torsade de Pointes, and in patients at increased risk of Torsade de Pointes.

Ipilimumab: Myositis

Japan – The PMDA has recommended to include a warning about the risk of muscle inflammation (myositis) in the product information for the skin cancer medicine ipilimumab (Yervoy®) in order to align it with the product information approved in the EU and the U.S.

Nintedanib: Liver injury

New Zealand, Canada – The marketing authorization holders, in agreement with Medsafe, have informed health professionals that cases of drug-induced liver injury (DILI), including one fatal case, have been reported in patients treated with nintedanib (Ofev®) in the post-marketing setting.\(^1, 2\) Most of these events occurred in the first three months of treatment.

Nintedanib is indicated for the treatment of idiopathic pulmonary fibrosis. The product information is being updated to reflect the observed increased severity of
DILI and to provide further guidance on the monitoring schedule of hepatic laboratory testing. Similar updates have been included in the product information approved in the U.S., the EU and Japan.


**Valproate:**

**Updated measures to avoid use in pregnancy**

**European Union** – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has recommended additional measures to avoid the use of valproate in pregnant women. The medicine should only be used in women of childbearing age if the conditions of a new pregnancy prevention programme are met. New visual warnings, a patient reminder card and updated educational materials will also be introduced to warn about the risk of malformations and developmental problems in infants exposed to valproate in the womb. The PRAC recognized that for some pregnant women with epilepsy it may not be possible to stop valproate, and determined that they can continue treatment with appropriate specialist care.

Valproate is used in the EU to treat epilepsy and bipolar disorder. In some EU member states it is also authorized to prevent migraine headaches. The measures taken following an earlier review have not been sufficient to mitigate the risks of valproate in pregnancy. The strengthened warnings were adopted following a second review with wide consultation, including a public hearing.


**Opioid cough and cold medicines: Labelling changes**

**United States of America** – The FDA is requiring updates to the product information for prescription cough and cold medicines containing codeine or hydrocodone to limit the use of these products to adults 18 years and older and to provide information about the risks of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing. The updates are based on the outcome of an FDA review communicated in April 2017 and the recommendations of an expert panel.

1. FDA Drug safety communication, 11 January 2018.

**Idarucizumab:**

**Second dose may be needed**

**New Zealand** – Following the outcome of a full cohort study, Medsafe has alerted health professionals that some patients may need a second dose of idarucizumab (Praxbind®) to reverse the effects of dabigatran (Pradaxa®). The timing of the second dose depends on the timing of the recurrence of bleeding and the measurement of the elevated coagulation tests. More information is shown in the product’s data sheet. Idarucizumab is indicated in patients treated with dabigatran when rapid reversal of dabigatran’s anticoagulant effect is required for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding.


**Gadolinium-based contrast agents**

**United States of America** – Based on results of an additional review the FDA is requiring a new class warning for gadolinium-based contrast agents, alerting health professionals and patients to the risks caused by long-term gadolinium retention in the body. A
patient medication guide will be introduced, and manufacturers have been requested to conduct further human and animal safety studies.\(^1\)

In the EU a final decision on restrictions for linear gadolinium-based contrast agents has been published following the conclusion of the EMA’s regulatory review in July 2017. The restrictions recommended earlier were maintained.\(^2\)

\(^1\) FDA Drug safety communication, 19 December 2017.

\(^2\) EMA’s final opinion confirms restrictions on use of linear gadolinium agents in body scans, 23 November 2017.

**Interim recommendations**

**Ulipristal:**

No new treatment courses to be started

European Union – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that, pending the outcome of its ongoing review of ulipristal (Esyma®), no patients should start new or repeat treatment courses with ulipristal for uterine fibroids. In women currently on treatment, liver function should be monitored at least once a month. If liver enzyme levels are more than twice the upper limit of normal, treatment should be stopped and the patient closely monitored, and the liver function tests should be repeated 2–4 weeks after stopping treatment.

Ulipristal is under EMA review following reports of serious liver injury, including liver failure leading to transplantation.

\(^1\) EMA Press release, 9 February 2018.

**Recombinant live-attenuated dengue vaccine**

WHO has published its interim position on the use of the recombinant, live-attenuated dengue vaccine Dengvaxia®.\(^1\) Vaccination is recommended only in individuals with a past dengue infection, as documented either by a diagnostic test or by a documented medical history of past dengue illness. This follows a review of preliminary results provided by the manufacturer. Further WHO guidance on the matter is expected no earlier than April 2018.

In 2016 the WHO Strategic Advisory Group of Experts on Immunization (SAGE) had recommended the vaccine for use in endemic areas with a seroprevalence over 70%.\(^2\) A theoretical elevated risk of dengue in vaccinated seronegative individuals was noted, prompting additional research by the manufacturer. Preliminary findings suggest that the subset of trial participants who had not been exposed to dengue virus prior to vaccination had a higher risk of more severe dengue and hospitalizations than unvaccinated participants. This increased risk was seen after an initial protective period and persisted over the observation period of up to 66 months after primary vaccination.

Dengvaxia® has been introduced in subnational programmes in the Philippines and Brazil targeting about one million individuals in total. It is otherwise available on the private market in countries where there is a marketing authorization. The manufacturer has proposed a labelling change to the national regulatory authorities in the countries where Dengvaxia® is licensed.

\(^1\) WHO. Updated Questions and Answers related to the dengue vaccine Dengvaxia® and its use. 22 December 2017.


**Radium-223 dichloride:**

Must not be used with abiraterone and prednisone / prednisolone

European Union – The EMA has recommended contraindicating the
use of the prostate cancer medicine radium-223 dichloride (Xofigo®) with abiraterone (Zytiga®) and prednisone / prednisolone due to an increased risk of death and fractures. Healthcare professionals should stop this combination in men currently treated with it and review the treatment for these patients. The safety and efficacy of radium-223 in combination with second-generation androgen receptor antagonists, such as enzalutamide (Xtandi®), have not been established.

The contraindication was introduced by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) as a temporary measure in view of the seriousness of the events reported in a clinical trial. An in-depth review of the benefits and risks of radium-223 is ongoing.


### Warnings softened

**Direct-acting antivirals:** Effect on blood glucose not confirmed

New Zealand – Medsafe has provided an update on its monitoring communication issued in March 2017, which highlighted a possible blood glucose-lowering effect of the direct acting antivirals Viekira Pak® and Viekira Pak-RBV® when used in patients with type 2 diabetes. No further cases were reported in New Zealand, and the effect could not be confirmed.

► Medsafe monitoring communication, 31 January 2018.

**Mycophenolate:** Updated recommendations for contraception

European Union – The EMA has updated its recommendations for contraception in men and women taking mycophenolate-containing medicines to prevent rejection of transplanted organs. The previous recommendation that male patients should use condoms in addition to their female partners using a highly effective method of contraception has been removed. Either the male patient or his female partner should use reliable contraception during mycophenolate treatment and for at least 90 days after stopping treatment. Female patients who can become pregnant must use at least one reliable form of contraception before, during and for 6 weeks after stopping treatment. Two forms of contraception are preferred but no longer mandatory.


### Combination treatments for asthma: Warning removed

United States of America – An FDA review of four large clinical safety trials has shown that treating asthma with long-acting beta agonists (LABAs, e.g. salmeterol, vilanterol, formoterol) in combination with inhaled corticosteroids (ICS, e.g. fluticasone, mometasone, budesonide) does not result in significantly more serious asthma-related side effects than treatment with an ICS alone. The Boxed Warning about asthma-related death has been removed from the product information of medicines that contain both an ICS and LABA.

Using LABAs alone to treat asthma without an ICS to treat lung inflammation is associated with an increased risk of asthma-related death. The warnings stating this will remain in the product information of the relevant medicines.

► FDA Drug safety communication, 20 December 2017.
## Reviews started

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Use</th>
<th>Concerns</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daclizumab</strong></td>
<td>Treatment of multiple sclerosis</td>
<td>Cases of serious inflammatory brain disorders, including 3 fatal cases. Linked to potentially fatal immune-mediated liver injury in a 2017 review. Possible risk of other immune-mediated disorders. <strong>To be recalled</strong> (see page 20).</td>
<td>► EMA Press release, 7 March 2017.</td>
</tr>
<tr>
<td><em>(urgent review)</em></td>
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<td><em>(Zinbryta</em>)</td>
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<tr>
<td><strong>Dabigatran</strong></td>
<td>Anti-thrombotic agent</td>
<td>Possible risk of gout or gout-like symptoms (one case report in New Zealand, and reports in WHO's VigiBase)</td>
<td>► Medsafe Monitoring Communication, 31 January 2018.</td>
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<tr>
<td><em>(Pradaxa</em>)</td>
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## Compliance with good practices

**Svizera Labs Pvt Ltd:**
**Notice of Concern withdrawn**
Following corrective actions taken by Svizera Labs Pvt Ltd and the clarifications provided being considered acceptable, and considering the outcome of an additional on-site inspection on 25–29 June 2017, the WHO Prequalification Team - Medicines has withdrawn the Notice of Concern (NOC) for Svizera Labs Pvt Ltd Mumbai, India. The NOC had been issued on 2 September 2015 after an inspection of the company’s site at Turbhe, Navi Mumbai, India.  

**Qinhuangdao Zizhu Pharmaceutical Co Ltd:**
**Corrective action under way**
Geneva – The WHO Prequalification Team-Medicines has provided an update on the level of compliance with good manufacturing practices (GMP) by Qinhuangdao Zizhu Pharmaceutical Co Ltd. On 8 March 2017 the U.S. FDA had placed an import alert on the company, following observations of serious breaches of data integrity and other GMP failures during an inspection of the company’s site located at No. 10, Longhai Avenue, in Qinhuangdao, Hebei Province, China.  
A WHO inspection of the site in December 2017 revealed that the company had only partly addressed the FDA’s observations. A follow-up WHO inspection is planned for October 2018 to verify that the company has implemented its corrective and preventive action (CAPA) plan as submitted to WHO.  
Qinhuangdao Zizhu manufactures three prequalified active pharmaceutical ingredients (APIs) – levonorgestrel, mifepristone and ethinylestradiol – and supplies levonorgestrel for two prequalified finished products. To date WHO has not received any complaints relating to the quality of prequalified levonorgestrel tablets. WHO is working closely with the manufacturers of prequalified levonorgestrel tablets to identify alternative API sources, and has requested them to take additional measures to ensure that all API batches from Qinhuangdao Zizhu meet their specifications.  
Falsified cefixime products circulating in the Democratic Republic of the Congo

The WHO Medical Product Alert No. 1/2018 relates to two versions of falsified cefixime products that have been identified in the eastern part of the Democratic Republic of the Congo (South Kivu) and were reported to WHO in late 2017. Cefixime is used to treat a range of bacterial infections and is listed as a WHO Essential Medicine.

The products were sent for quality assurance laboratory testing and the results shared with WHO (see table). Both products are presented in standard white plastic containers of 100 tablets. The tablets of both products are round, small, and without any embossing. The labels of both products have spelling mistakes. Product details are shown below.

<table>
<thead>
<tr>
<th>Product 1</th>
<th>Product 2</th>
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<tbody>
<tr>
<td>Product name:</td>
<td>CEFIXIME</td>
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<tr>
<td>Batch number:</td>
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<tr>
<td>Expiry date:</td>
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<tr>
<td>Manufacturing date:</td>
<td>01/2016</td>
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<tr>
<td>Stated active pharmaceutical ingredient:</td>
<td>Cefixime</td>
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<tr>
<td>Manufacturer name stated on the label:</td>
<td>MERCK &amp; CO. INC.</td>
</tr>
<tr>
<td>Assay result:</td>
<td>2.5% of declared content of cefixime</td>
</tr>
</tbody>
</table>

Both stated manufacturers have confirmed they did not manufacture either of these products. No adverse reactions to either product have been reported to WHO at this stage.

► WHO Medical Product Alert No. 1/2018 (includes photographs).

Falsified “Augmentin” circulating in Cameroon

The WHO Medical Product Alert No. 2/2018 relates to a falsified version of Augmentin (amoxicillin + clavulanate potassium) identified in Cameroon. WHO was informed in early 2018 by an NGO that this product was available in a street market in Douala. The packaging of the falsified product appears to be a close imitation of the genuine product manufactured by GlaxoSmithKline (GSK). The writing on the packaging has some spelling errors. GSK has confirmed that they did not manufacture this product.

Samples were sent for quality assurance testing and the results shared with WHO. The laboratory analysis did not identify any of the expected active ingredients.

The source of the falsified product has not yet been identified. No adverse reactions have been reported to WHO at this stage.

► WHO Medical Product Alert No. 2/2018 (includes photographs).

Report suspected falsified products to the competent national regulatory authority and/or pharmacovigilance centre, and notify WHO at rapidalert@who.int.