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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 regulatory information on the safety 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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This Newsletter is also available at:
http://www.who.int/medicines

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 the WHO global database of individual case safety reports, VigiBase.

This edition of the Newsletter includes highlights from the 42nd Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring, a brief report on the Advanced Pharmacovigilance workshop organized by WHO and updates on the WHO implementation of an ADR Reporting App in countries.

Contents

Regulatory matters

Safety of medicines

Signal

Feature

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Table of Contents

Regulatory Matters

Alemtuzumab 5
Apalutamide, Enzalutamide 5
Baricitinib 5
Belimumab 5
Carfilzomib 5
Cefotaxime 6
Chloroquine 6
Dabigatran 6
Epirubicin 6
Estradiol 7
Fluoroquinolones, quinolones (oral, injectable) 7
Ingenol mebutate (gel) 7
Moxifloxacin 8
Osimertinib mesilate 8
Pentosan polysulfate sodium 8
Proton pump inhibitors (PPIs) 8
D-Sorbitol 9
Tocilizumab 9
Tofacitinib 9
Vonoprazan 10
Yellow fever vaccine 10

Safety of medicines

Fingolimod 11
Montelukast 11
Nivolumab 11

Signal

Levonorgestrel-releasing intrauterine device and panic attacks: a signal raised in patient reporting 12
Nintedanib and ischaemic colitis 18

Feature

42nd Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring 25

Table of Contents

Advanced Pharmacovigilance workshop on Causality assessment, signal detection and benefit risk analysis..... 26

Med Safety App: an international mobile tool for drug safety 27

Alemtuzumab

Risk of cardiovascular disorders and immune-related disorders

Europe. The European Medicines Agency (EMA) has recommended that the use of alemtuzumab (Lemtrada®) should be restricted. It should be used to treat relapsing-remitting multiple sclerosis, only if the disease is highly active despite treatment with at least one disease-modifying therapy or if the disease is worsening rapidly. The restriction is due to reports of rare but serious cardiovascular disorders.

Alemtuzumab is indicated to treat adults with relapsing-remitting multiple sclerosis.

The EMA has also recommended updating the physician's guide and the patient information pack with advice on minimising the risk of serious cardiovascular disorders. These recommendations were issued by the Pharmacovigilance Risk Assessment Committee (PRAC) and have now been endorsed by the Committee for Medicinal Products for Human Use (CHMP).

Reference:
EMA, 15 November 2019 *(www.ema.europa.eu)*

(See WHO Pharmaceuticals Newsletter No.4, 2019: Risk of serious cardiovascular and immune-mediated adverse reactions in UK; No.3, 2019: Cardiovascular and immune-mediated adverse effects in EU)

Apalutamide, Enzalutamide

Risk of interstitial lung disease

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for apalutamide (Erleada®) and enzalutamide (Xtandi®) should be revised to include interstitial lung disease as an adverse drug reaction.

Apalutamide and enzalutamide are indicated for castration-resistant prostate cancer.

A total of four cases of interstitial lung disease occurring in patients taking apalutamide have been reported in Japan during the previous three fiscal years. One of these cases was fatal and a causal relationship could not be excluded. Additionally, 19 cases of interstitial lung disease in patients taking enzalutamide have been reported in Japan. Three of these cases were fatal and a causal relationship could not be established.

Reference:
Revision of Precautions, MHLW/PMDA, 15 November 2019 *(www.pmda.go.jp/english/)*

Baricitinib

Risk of venous thromboembolism

Japan. The MHLW and the PMDA have announced that the package insert for baricitinib (Olumiant®) should be revised to include venous thromboembolism as an adverse drug reaction.

Baricitinib is indicated to treat rheumatoid arthritis in patients who have had an inadequate response to conventional treatments.

A total of five cases of venous thromboembolism have been reported during the previous three fiscal years in Japan, and for one case a causal relationship between baricitinib and the event could not be excluded. No patient mortalities have been reported.

Reference:
Revision of Precautions, MHLW/PMDA, 24 September 2019 *(www.pmda.go.jp/english/)*

Belimumab

Risk of depression, suicidal ideation, and suicide attempt

Japan. The MHLW and the PMDA have announced that the package insert for belimumab (Benlysta®) should be revised to include depression, suicidal ideation and suicide attempt as adverse drug reactions.

Belimumab is indicated for systemic lupus erythematosus in patients who have had an inadequate response to conventional treatment.

Results of post-marketing clinical study conducted in systemic lupus erythematosus patients suggested higher incidences of depression, suicide and/or self-injury in the group administered belimumab plus standard therapy such as steroid therapy, compared with the group administered placebo and standard therapy. The MHLW and the PMDA have concluded that the revision of the package insert was necessary.

One case involving depression, suicidal ideation and suicidal attempt has been reported in Japan during the previous three fiscal years.

Reference:
Revision of Precautions, MHLW/PMDA, 29 October 2019 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.3, 2019: Risk of serious psychiatric events in UK)

Carfilzomib

Risk of reactivation of hepatitis B virus (HBV)

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that changes are being made to the Summary of Product Characteristics of carfilzomib (Kyprolis®) to recommend

screening for hepatitis B virus (HBV) before initiation of treatment.

Carfilzomib is indicated in combination with lenalidomide and dexamethasone or with only dexamethasone for the treatment of multiple myeloma.

A recent EU review has identified reports of HBV reactivation associated with carfilzomib. The review assessed cases worldwide up to 10 July 2019 and identified 23 cases of HBV reactivation from clinical studies and post-marketing information.

Health-care professionals should screen all patients for HBV before initiation of carfilzomib and consider prophylaxis with antivirals for patients with positive serology who are treated with carfilzomib. Also, health-care professionals should advise patients with a positive serology to seek medical help immediately if they experience signs and symptoms suggestive of HBV reactivation.

Reference:
Drug Safety Update, MHRA, 21 November 2019 (*www.gov.uk/mhra*)

Cefotaxime

Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome

Republic of Korea. The Ministry of Food and Drug Safety (MFDS) of Korea has updated the drug label for cefotaxime (Claforan®) to include the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Cefotaxime is an injectable third-generation cephalosporin used to treat a variety of bacterial infections.

During the evaluation process of reports of serious adverse events (SAE), the Korea Institute of Drug safety and Risk Management (KIDS) reviewed three SAE reports of DRESS syndrome in association with exposure to cefotaxime.

At the time of review, KIDS had received nine domestic and 24 international reports of DRESS syndrome with cefotaxime use through the Korean Adverse Event Reporting System (KAERS) since 1989. Case evaluation was performed on these reports, and a causal association could not be excluded.

This recommendation announced by MFDS was based on the results of the SAE review system, signal analysis and evaluation process at KIDS.

Reference:
Based on the communication from MFDS and KIDS, Republic of Korea, October 2019

Chloroquine

Risk of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)

India. The National Coordination Centre - Pharmacovigilance Programme of India (NCC-PvPI) has made a recommendation to the Central Drugs Standard Control Organisation (CDSCO) for the revision of the patient information leaflet (PIL) for chloroquine to incorporate Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) as clinically significant adverse drug reactions.

Chloroquine is used for the treatment of malaria. Between July 2011 and April 2019, the NCC-PvPI received eight individual case safety reports (ICSRs) of chloroquine associated TEN and 10 ICSRs of SJS. The cases were reviewed by the Signal Review Panel (SRP), PvPI and IPC which found a strong causal relationship between chloroquine associated SJS/TEN.

Reference:
Based on the communication from NCC-PvPI, IPC India (*ipc.gov.in*)

Dabigatran

Risk of vasculitis

New Zealand. Medsafe is placing dabigatran (Pradaxa®) on the Medicines Monitoring scheme following a report of vasculitis and rash.

Dabigatran is indicated for the prevention of stroke, systemic embolism, venous thromboembolic events, reduction of vascular mortality and treatment of acute deep vein thrombosis and/or pulmonary embolism.

In New Zealand, four reports describing suspected vasculitis or vasculitic rash with dabigatran use have been reported since 2012 until September 2019.

Reference:
Safety Communication, Medsafe, 14 November 2019 (*www.medsafe.govt.nz/*)

(See WHO Pharmaceuticals Newsletter No.5, 2019: Risk of recurrent thrombotic events in Australia and New Zealand; No.4, 2019: Increased risk of recurrent thrombotic events in UK; No.3, 2016: Risk of thrombocytopenia in Japan; No.2, 2016: Benefit-risk balance of rivaroxaban: unchanged in EU; No.6, 2013: Apixaban, dabigatran and rivaroxaban in UK)

Epirubicin

Risk of pneumonia

Republic of Korea. The MFDS has updated the drug label for epirubicin (Pharmorubicin®) to include pneumonia as an adverse drug reaction.

Epirubicin, a derivative of doxorubicin, is an

antineoplastic agent. It is used as a component of various chemotherapy regimens to treat breast cancer, gastric cancer, Hodgkin's disease, malignant tumor of nasopharynx.

During the evaluation process of serious adverse event reports, KIDS reviewed a fatal SAE report of *Pneumocystis jirovecii* pneumonia in a patient who was receiving epirubicin-containing chemotherapy. Causal association could not be excluded between epirubicin and pneumonia in this case.

This recommendation announced by the MFDS was based on the results of the SAE review system at KIDS.

Health-care professionals should be reminded of the myelosuppressive effects of epirubicin and are advised to monitor for any signs of serious infections during use of this drug.

Reference:
Based on the communication from MFDS and KIDS, Republic of Korea, October 2019

Estradiol

Four-week limit for use of high strength estradiol creams

Europe. The EMA has announced that the PRAC has recommended limiting the use of high-strength estradiol containing creams to a single treatment period of up to four weeks.

Estradiol-containing creams are used in topical hormone replacement therapy (HRT). It is indicated to treat symptoms of vaginal atrophy in postmenopausal women. The adverse drug reactions of HRT taken orally or used transdermally include venous thromboembolism, stroke, endometrial cancer and breast cancer.

High-strength estradiol creams should not be prescribed for longer than a single treatment period of four weeks.

Reference:
EMA, 4 October 2019 *(www.ema.europa.eu)*

Fluoroquinolones, quinolones (oral, injectable)

Risk of tendon disorders, peripheral neuropathy and psychiatric symptoms

Japan. The MHLW and the PMDA have announced that the package inserts for fluoroquinolones and quinolones should be revised to include tendon disorders, peripheral neuropathy and psychiatric symptoms as adverse drug reactions.

Fluoroquinolones and quinolones are antibacterials, indicated for conditions such as superficial skin infections, thermal burn, tonsillitis, acute bronchitis and pneumonia. Examples of fluoroquinolones include levofloxacin (Cravit®), moxifloxacin (Avelox®), ofloxacin (Tarivid®) and pipemidic acid (Dolcol®).

The MHLW/PMDA decision follows the European and US revisions to the package insert. It is thought that collagen tissue disorders and suppression of GABA nerves were potential mechanisms of onset of tendon disorders and psychiatric symptoms. These mechanisms and risks are common to all the antibacterials of this class.

Currently there is not enough information on the mechanism of action for peripheral neuropathy or epidemiological information to indicate that this event is a risk common to all fluoroquinolones and quinolones, but cases have been reported in Japan in patients treated fluoroquinolones such as levofloxacin.

MHLW and PMDA have concluded that revision of the package insert was necessary to include a precaution in all fluoroquinolone and quinolone antibacterials based on the results of the investigation.

Reference:
Revision of Precautions, MHLW/PMDA, 24 September 2019 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.3, 2019: Risk of musculoskeletal and nervous systems damage in UK; No.1, 2019: Risk of tendon damage and neuropathies in Ireland; No.6, 2018: Risk of long-lasting and disabling effects in Europe; No.2, 2017: Potential risk of persistent and disabling side effects in Canada; No.5, 2016: Disabling and potentially permanent adverse effects of the tendons, muscles, joints, nerves, and central nervous system in USA)

Ingenol mebutate (gel)

Increased incidence of skin tumours

United Kingdom. The MHRA has announced that the product information for ingenol mebutate gel (Picato®) is being updated to include a warning about reports of basal cell carcinoma, Bowen's disease and squamous cell carcinoma.

Ingenol mebutate gel is indicated for the treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults.

A European review on ingenol mebutate has begun following several studies showing an increased number of skin cancer cases in patients using ingenol mebutate gel.

A warning about the risk of keratoacanthoma was previously included in the product information, but following a separate review of safety data, the product information is being updated.

Since 2013 and up to August 2019, the MHRA received nine cases of skin malignancies with ingenol mebutate, including cutaneous squamous cell carcinoma, atypical fibroxanthoma, neuroendocrine carcinoma of the skin, Bowen's disease, and basosquamous carcinoma.

Health-care professionals should advise patients using ingenol mebutate gel to be vigilant for the development of any new skin lesions within the treatment area and to seek medical advice immediately. Also, health-care professionals should use the drug with caution in patients with a history of skin cancer.

Reference:
Drug Safety Update, MHRA, 18 October 2019 *(www.gov.uk/mhra)*

(See WHO Pharmaceuticals Newsletter No.5, 2019: Potential risk of skin cancer in EU; No.3, 2017: Risk of hypersensitivity reactions, herpes zoster and eye injury in Australia; No.5, 2015: Risk of severe allergic reactions and herpes zoster (shingles) in the USA)

Moxifloxacin

Risk of acute generalized exanthematous pustulosis (AGEP)

Republic of Korea. The MFDS has updated the drug label for oral moxifloxacin (Avelox®) to include the risk of acute generalized exanthematous

During the evaluation process of serious adverse event reports, the KIDS reviewed one fatal SAE report of AGEP in a patient who was receiving moxifloxacin-containing tuberculosis treatment regimen.

At the time of review, KIDS had received three domestic reports of AGEP with the use of moxifloxacin through the Korean Adverse Event Reporting System KAERS since 1989. Case evaluation was performed on these reports, and a causal association could not be excluded between moxifloxacin and AGEP.

This recommendation announced by MFDS was based on the results of SAE review system and signal analysis evaluation process at KIDS.

Reference:
Based on the communication from MFDS and KIDS, Republic of Korea, October 2019

Osimertinib mesilate

Risk of TEN, Stevens-Johnson syndrome (SJS), erythema multiforme

Japan. The MHLW and the PMDA have announced that the package insert for osimertinib mesilate (Tagrisso®) should be revised to include TEN, oculomucocutaneous syndrome (Stevens-Johnson syndrome, SJS) and erythema multiforme

MHLW and PMDA have concluded that revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Reference:
Revision of Precautions, MHLW/PMDA, 24 September 2019 *(www.pmda.go.jp/english/)*

Pentosan polysulfate sodium

Rare risk of pigmentary maculopathy

United Kingdom. The MHRA has announced that the product information for pentosan polysulfate (Elmiron®) has been updated to include rare risk of pigmentary maculopathy.

Pentosan polysulfate is indicated for the treatment of bladder pain syndrome (interstitial cystitis) with moderate to severe pain, urgency and frequency of micturition.

Health-care professionals should advise patients on pentosan polysulfate to promptly seek medical advice in case of visual changes such as reading difficulty or slow adjustment to low or reduced light environments. Also, discontinuation of the treatment should be considered in patients with pigmentary maculopathy.