2015

KIMS PHARMACOVIGILANCE

DRUG UPDATES, NEWS AND VIEWS

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CONTENTS

US FDA — NEW DRUG APPROVALS

1. IVABRADINE—CHRONIC HEART FAILURE

IVABRADINE is a hyperpolarization-activated cyclic nucleotide-gated channel blocker that selectively inhibits the I_f-current, which is a mixed Na^+-K^+ inward current highly expressed in the SAN and regulating the heart rate. I_f is activated by hyperpolarization and modulated by the ANS, resulting in heart rate reduction with no effect on ventricular repolarization and no effects on myocardial contractility.

IVABRADINE is currently used for the symptomatic management of stable angina pectoris, and it is recently approved to prevent worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤35%, who are in sinus rhythm with resting heart rate ≥70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

Formulation: Available as tablets of 5 mg to be taken twice daily, dose adjusted after 2 weeks based on heart rate to a maximum dose of 7.5 mg twice daily, a smaller dose (2.5 mg) in patients with conduction defects.

Adverse events: Bradycardia, hypertension, atrial fibrillation and luminous phenomena (sensation of enhanced brightness in a fully maintained visual field).

US FDA approval: April 2015.

2. CANGRELOR—ANTIPLATELET AGENT

CANGRELOR is a direct P2Y12 platelet receptor inhibitor that blocks ADP-induced platelet activation and aggregation. CANGRELOR binds selectively and reversibly to the P2Y12 receptor to prevent further signaling and platelet activation.

CANGRELOR is specifically indicated as an adjunct to percutaneous coronary intervention for reducing the risk of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a P2Y12 platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.

Formulation: Available as lyophilized powder for IV infusion at a dose of 30 mcg/kg IV bolus followed immediately by 4 mcg/kg/min IV infusion prior to PCI and infusion maintained for at least 2 hours or for the duration of PCI, whichever is longer.

Adverse events: Bleeding.

US FDA approval: June 2015.

3. ISAVUCONAZONIUM SULFATE

ISAVUCONAZONIUM SULFATE is the prodrug of isavuconazole, an azole antifungal drug, which inhibits synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14-alpha-demethylase.

ISAVUCONAZONIUM SULFATE is specifically indicated for patients ≥18 years for the treatment of invasive aspergillosis and invasive mucormycosis.

Formulation: Available as solution for IV infusion and as capsule for oral administration at a recommended loading dose of 372 mga every 8 hours and a maintenance dose of 372 mga once daily

Adverse events: Nausea, vomiting, diarrhea, headache, abnormal liver blood tests, hypokalemia, constipation, dyspnea, coughing and peripheral edema. Serious side effects include liver problems, infusion reactions and severe allergic and skin reactions.

US FDA approval: March 2015.

4. DEOXYCHOLIC ACID

DEOXYCHOLIC ACID is a non-human and non-animal formulation of deoxycholic acid, a naturally-occurring molecule in the body that aids in the breakdown and absorption of dietary fat. When injected into subcutaneous fat, it causes destruction of fat cells, leaving surrounding tissue largely unaffected.

DEOXYCHOLIC ACID is indicated for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults.

Formulation: Available as SC injection used at an area-adjusted dose of 2 mg/cm^2.

Adverse events: Injection site edema/swelling, hematoma, pain, numbness, erythema and induration.

FDA approval: April 2015.

5. ELUXADOLINE

ELUXADOLINE is a μ-opioid receptor agonist and δ-opioid receptor antagonist, which can control the GI function, decreasing pain and avoiding excessive constipation from unopposed μ-agonism.

ELUXADOLINE is specifically indicated in adults for the treatment of irritable bowel syndrome with diarrhea.

Formulation: Available as a tablet to be taken at a dose of 100 mg orally twice daily with food.

Adverse events: Constipation, nausea, abdominal pain.

US FDA approval: May 2015.

EMA — NEW DRUG APPROVALS

6. SAFINAMIDE

SAFINAMIDE is an anti-Parkinson's drug with multiple mechanisms of action. It is a highly selective and reversible MAO-B inhibitor causing an increase in extracellular levels of dopamine in the striatum. It is also associated with state-dependent inhibition of voltage-gated Na+ channels, and modulation of stimulated release of glutamate. Additionally, it blocks calcium channels.

SAFINAMIDE has been approved by the EMA for the treatment of adult patients with idiopathic Parkinson's disease as add-on therapy to a stable dose of levodopa alone or in combination with other drugs in patients with mid-to-late-stage fluctuating disease.

Other potential uses include restless legs syndrome (RLS) and epilepsy.

Formulation: Film-coated tablets at a dose of 50-100 mg daily.

Adverse events: Dyskinesia, somnolence, dizziness, headache, insomnia, nausea and orthostatic hypotension.

EMA (CHMP) approval: December 2014.

7. SONIDEGIB

SONIDEGIB is an antineoplastic agent, which inhibits the Hedgehog pathway, a key regulator of development and morphogenesis in mammals, which is linked to the pathogenesis of several cancers including BCC.

SONIDEGIB is indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy.

Formulation: Available as 200 mg hard capsules.

Adverse events: Muscle cramps, muscle pain, hair loss, alteration or loss of taste, nausea, diarrhea, increased creatine phosphokinase, decreased weight and fatigue.

EMA (CHMP) approval: June 2015.

DRUG SAFETY ALERTS

8. DOMPERIDONE—CARDIAC SAFETY

DOMPERIDONE-containing medicines have a small increased risk of adverse cardiac effects, which may be higher in patients over 60 years or at total daily doses of more than 30 mg. Maximum recommended dose has been reduced from 80 mg to 40 mg daily. Because of the safety concern, it is now contraindicated by HEALTH CANADA in patients with prolonged of cardiac conduction intervals, significant electrolyte disturbances, cardiac disease or liver impairment, and those receiving QT-prolonging drugs or potent CYP3A4 inhibitors.

DOMPERIDONE should be used at the lowest effective dose up to a maximum recommended daily dose of 30 mg and for the shortest possible duration.

9. AMBROXOL/BROMHEXINE—RARE SEVERE SKIN REACTIONS

AMBROXOL and BROMHEXINE are the commonly used mucokinetic and mucolytic agents. As there are reports of severe cutaneous adverse reactions (SCARs) such as erythema multiforme and Stevens-Johnson syndrome, though rare, the Coordination Group for Mutual Recognition and Decentralised Procedures–Human (CMDh) – a regulatory body representing EU Member States has endorsed recommendations to add information about a small risk of severe allergic reactions including SCARs, to the product information for AMBROXOL and BROMHEXINE containing medicines. The recommendations originated from EMA's (PRAC), whose review of the two medicines confirmed the known risk of allergic reactions and identified a small risk of SCARs.

10. NITROFURANTOIN—RENAL IMPAIRMENT

The efficacy of NITROFURANTOIN in treating and preventing UTIs depends on its renal secretion into the urinary tract. The Medicines and Healthcare Products Regulatory Agency (MHRA) has recommended that NITROFURANTOIN be allowed in patients with an eGFR of 45 ml/min/1.73m^2 or more (previously: 60 ml/min/1.73m^2). The revised recommendations consider the fact that lower urinary tract pathogens are increasingly resistant to standard therapy (TRIMETHOPRIM and AMOXICILLIN), and that the widespread use of alternative broad spectrum antibiotics (CEPHALOSPORINS and FLUOROQUINOLONES) is associated with the risk of *Clostridium difficile* colitis.

11. RISPERIDONE IN VASCULAR OR MIXED-TYPE DEMENTIA

HEALTH CANADA has restricted the indication for RISPERIDONE in dementia to the short-term symptomatic management of aggression or psychotic symptoms in patients with severe dementia of the Alzheimer type unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others. The indication no longer includes the treatment of other types of dementia. The recommendation is based on available safety information on antipsychotic drugs, indicating a higher risk of cerebrovascular adverse events in patients with mixed and vascular dementia compared to those with dementia of the Alzheimer type.

12. HYDROXYZINE—NEW RESTRICTIONS

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has completed a review of medicines containing the antihistamine HYDROXYZINE. These are available in most EU countries for various indications such as treatment of anxiety disorders and sleep disorders, relief of itching caused by urticaria, and as premedication before surgery. The PRAC considered that HYDROXYZINE is associated with a small but definite risk of QT interval prolongation and torsade de pointes, which can lead to abnormal heart rhythms and cardiac arrest and hence to be used in the minimum effective dose for the shortest possible duration. The maximum daily dose should be no more than 100 mg in adults (50 mg in the elderly if use cannot be avoided), and 2 mg/kg body weight in children up to 40 kg body weight. Use must be avoided in patients who have risk factors for arrhythmias or are taking other medicines associated with QT prolongation; care is needed in patients taking medicines that slow the heart rate or decrease blood potassium levels.

13. CODEINE-CONTAINING COUGH AND COLD MEDICINES IN CHILDREN

Medsafe's Medicines Adverse Reactions Committee (New Zealand) has recommended to restrict the use of all CODEINE-containing cough and cold medicines in children aged ≤12 years. An EMA review of these medicines started in April 2014 following concerns of morphine-like toxicity including respiratory depression.

14. LINAGLIPTIN-POSSIBLE LIVER TOXICITY

LINAGLIPTIN is a DPP-4 inhibitor approved as an add-on therapy to control post-prandial hyperglycemia in type 2 DM. Following reports of hepatic dysfunction in patients treated with LINAGLIPTIN, the Pharmaceuticals and Medical Devices Agency (Japan) have recommended to update the product information to include this risk. Health professionals should monitor patients treated with LINAGLIPTIN for signs of liver dysfunction, including liver enzyme elevations, and should consider stopping LINAGLIPTIN in case of abnormalities.

15. APIXABAN—INTERSTITIAL LUNG DISEASE

APIXABAN is a potent, orally effective, highly selective inhibitor of factor Xa, preventing thrombin generation and thrombus formation. The PMDA (Japan) has recommended to revise the product information for APIXABAN following reported cases of hemorrhage and bloody sputum suggestive of interstitial lung disease, including suspected interstitial pneumonia in some cases.

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