Drug Information Bulletin

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Regulatory Affairs Division (RAD), IPA

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Content

Editorial

Recently Drugs Controller General of India requested all State/UT drugs controllers to take necessary measures for implementation of "Pharmacovigilance Guidance Documents for Marketing Authorization Holders of Pharmaceutical Products" published by Indian Pharmacopoeia Commission in collaboration with Central Drugs Standard Control Organization (CDSCO) from 01.01.2018 . The matter was drafted by an expert group and finalized after taking inputs from all stake holders.

Pharmacovigilance is required as per the provision of clause 28.2 of the Schedule M which stated that "Reports of serious adverse drug reactions resulting from the use of a drug along with comments and documents shall be forthwith reported to the concerned licensing authority". In a recent amendment it made mandatory to have a separate Pharmacovigilance system in place for collecting, processing, and forwarding the report to the licensing authority for information on adverse reactions emerging from the use of the drug manufactured or marketed by the applicant in the country. The system shall be managed by qualified and trained personnel and the officer in-charge of collection and processing of data shall be a medical officer or a pharmacist trained in collection and analysis of adverse drug reaction reports. This will help to ensure the safety of the product in the market. Hope all MAH will implement this mandate as they have done earlier.

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New Drug: Tenofovir Alafenamide tablets, for oral use (First approved by FDA in the brand name VEMLIDY)

WARNING: LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS and POST TREATMENT SEVERE ACUTE EXACERBATION OF HEPATITIS B See full prescribing information for complete boxed warning. • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs. (5.1) • Discontinuation of anti-hepatitis B therapy may result in severe acute exacerbations of hepatitis B. Hepatic function should be monitored closely in patients who discontinue VEMLIDY. If appropriate, resumption of anti-hepatitis B therapy may be warranted.

INDICATIONS AND USAGE: VEMLIDY is a hepatitis B virus (HBV) nucleoside analog reverse transcriptase inhibitor and is indicated for the treatment of chronic hepatitis B virus infection in adults with compensated liver disease.

DOSAGE AND ADMINISTRATION: • Testing: Prior to initiation of VEMLIDY, test patients for HIV infection. VEMLIDY alone should not be used in patients with HIV infection. Assess serum creatinine, serum phosphorous, estimated creatinine clearance, urine glucose, and urine protein before initiating VEMLIDY and during therapy in all patients as clinically appropriate. (2.1) • Recommended dosage: 25 mg (one tablet) taken orally once daily with food. (2.2) • Renal Impairment: VEMLIDY is not recommended in patients with estimated creatinine clearance below 15 mL per minute. (2.3) • Hepatic Impairment: VEMLIDY is not recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment.

DOSAGE FORMS AND STRENGTHS: Tablets: 25 mg of tenofovir alafenamide.

WARNINGS AND PRECAUTIONS: • HBV and HIV-1 coinfection: VEMLIDY alone is not recommended for the treatment of HIV-1 infection. HIV-1 resistance may develop in these patients. (5.3) • New onset or worsening renal impairment: Assessment of serum creatinine, serum phosphorus, estimated creatinine clearance, urine glucose, and urine protein is recommended before initiating VEMLIDY therapy and during therapy as clinically appropriate.

ADVERSE REACTIONS: Most common adverse reactions (incidence greater than or equal to 5%, all grades) are headache, abdominal pain, fatigue, cough, nausea, and back pain. (6.1) To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS: VEMLIDY is a substrate of P-glycoprotein (P-gp) and BCRP. Drugs that strongly affect P-gp and BCRP activity may lead to changes in VEMLIDY absorption. Consult the full prescribing information prior to and during treatment for potential drug-drug interactions.

Ref.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208464s000lbl.pdf

Status in India: Tenofovir Alafenamide Fumarate bulk & 25 mg capsules was approved by the CDSCO for the treatment of chronic Hepatitis B virus infection in adults with compensated liver disease on 10.11.2017.

Hyoscine butylbromide ampoule Caution of use in patients with pre-existing cardiac conditions

The Therapeutic Goods Administration (TGA) has updated product information for hyoscine butylbromide (Buscopan®) to include a caution regarding the use of hyoscine ampoules in patients with pre-existing cardiac conditions (for example cardiac failure, coronary heart disease). The Australian product information for hyoscine butylbromide already lists tachycardia, decreased blood pressure and anaphylaxis as potential adverse effects, but the product information has been updated to include a stronger warning in the precautions section because these adverse events can be more serious in patients with cardiac conditions. Monitoring of these patients is advised and

emergency equipment and personnel trained in its use must be readily available. Hyoscine butylbromide ampoules, administered by intramuscular or slow intravenous injection, are used to treat gastrointestinal tract, biliary and renal spasms, and are used as a diagnostic in radiology. There are 28 cases describing tachycardia and/or hypotension relating to use of hyoscine butylbromide in the TGA's adverse events database. An additional four cases describe anaphylactic reactions. There is insufficient clinical information provided to determine whether or not these reactions occurred in people with pre-existing cardiac conditions. None ofthese cases reported death, cardiac arrest or myocardial infarction.
Reference: Medicines Safety Update, TGA, Vol. 8, No. 4, August September 2017 (www.tga.gov.au)

Palivizumab Risk of thrombocytopenia

The MHLW and the PMDA have announced that the package insert for palivizumab (Synagis®) has been updated to include the risk of thrombocytopenia as aclinically significant adverse reaction. Palivizumab is indicated for: prevention of serious lower respiratory tract diseases caused by respiratory syncytial virus infection in high-risk neonates and infants and children. A total of four cases associated with thrombocytopenia have been reported in Japan. Of these, a causal relationship could not be excluded in one case.
Reference: Revision of Precautions, MHLW/PMDA, 12 September 2017 (www.pmda.go.jp/english/)

Warfarin Risk of calciphylaxis

The MHLW and the PMDA have announced that the package insert for warfarin has been updated to include the risk of calciphylaxis as a clinically significant adverse reaction. Warfarin is used for treatment and prevention of thromboembolism (including venous thrombosis, myocardial infarction, pulmonary embolism, brain embolism and, slowly progressive cerebral thrombosis). Eleven cases associated with calciphylaxis have been reported in Japan and there is an overseas report published in the literature describing calciphylaxis with the use of warfarin. In addition, package inserts in Europe and the United States have been revised.
Reference: Revision of Precautions, MHLW/PMDA, 8 August 2017 (www.pmda.go.jp/english/) (See WHO Pharmaceuticals Newsletters No.2, 2017: Risk of calciphylaxis in Malaysia and No.4, 2016: Reports of calciphylaxis in the US)

Teriflunomide Potential risk of acute renal injury or nephrolithiasis: not enough evidence

Health Canada has reviewed the potential risk of sudden onset of acute renal injury or nephrolithiasis with the use of teriflunomide (Aubagio®) following safety information received from the manufacturer. Teriflunomide is used to treat patients with multiple sclerosis (MS). At the time of the review, Health Canada received, 55 reports (all were international) of suspected sudden onset of kidney injury and 135 reports (eight of these were Canadian) of suspected nephrolithiasis with teriflunomide use from the manufacturer. No additional reports were found in Health Canada's Vigilance database. Upon review, only two reports of patients with sudden onset of renal injury were considered to be possibly related to the use of teriflunomide. The review of reports of nephrolithiasis did not show a link related to the use of teriflunomide. In these reports, other factors could have played a role, such as the MS itself or problems with the bladder. In addition, information in the reports that described the health of the patient's kidneys before taking teriflunomide was limited. In the published scientific literature, there were no reports or studies related to the possible association of sudden onset of renal injury or nephrolithiasis with the use of teriflunomide. There was limited evidence to suggest that MS patients may be at greater risk of renal injury or nephrolithiasis when taking teriflunomide. Health Canada's review of the available information did not establish a link

between the use of teriflunomide and a risk of sudden onset of renal injury or nephrolithiasis.
Reference: Summary Safety Review, Health Canada, 4 August 2017 (www.hc-sc.gc.ca)

CCI starts probe on alleged price fixing of key anti diabetic drugs

Competition Commission of India has initiated an investigation on drug makers Abbott, Novartis, Emcure Pharma and USV Pvt Ltd over alleged price fixing of the blockbuster anti-diabetic drug Vildagliptin, people aware of the development said.

The fair play regulator has sent notices to the four drug makers, asking them for trade details of this drug in an attempt to find out if the companies colluded with each other to keep the price of the drug at certain levels, they said. Competition Commission of India (CCI) is also looking at the involvement of senior executives from these companies over price fixing, sources said.
Vildagliptin, sold under the brand name Galvus, is a proprietary drug of Novartis that comes under the new class of antidiabetic drugs known as DPP 4 inhibitors. These drugs are prescribed for patients with Type 2 diabetes and are considered to be far more effective in controlling blood glucose level compared to the older class of drugs. Novartis, which reported revenues worth Rs 397 crore this year for this drug, has licensed the marketing rights to Abbott, Emcure and USV. This year, the combined brand of Vildagliptin recorded a sales worth Rs 790 crore, in the Rs 2,600-crore gliptin market.

The whistle-blower had reached out to several Indian regulators in February alleging that Novartis controls the pricing structure for Vildagliptin and that is followed by the other license holders, where the drug prices are matched to the lowest decimal. Though there is no written communication between partners, these companies also synchronise every price change, the person alleged. To back these claims, the whistle-blower had sent a chart that listed the various dosage size of these brands, and all of them were priced in the same range.
Price cartelisation is prohibited under the Competition Act, 2002.

Antitrust lawyers that ET spoke to said that though cartel enforcement has been a focus of CCI since the beginning, it has taken time to gain traction.

Estimates suggest that CCI has investigated several cases of cartels (including in pharmaceuticals sector), imposing a fine of more than Rs 7,500 crore on various companies and their officers.
Ref.
https://health.economictimes.indiatimes.com/news

Forthcoming Events:

69th Indian Pharmaceutical Congress
22nd – 24th December 2017
Venue: Chitkara University, Rajpura, Punjab
Contact: 69ipc.com

Annual get together
IPA Bengal Branch
Date: 7th January 2018 (Sunday)
Venue: AU Garden, Near Fultala, 24 pgs (South)
Contact:
Convenors-
Mr. Ashok Kumar Maity, Mob. 9433579919
Mr. Prabir Kumar Banerjee, Mob. 9433559974