



# Drug Information Bulletin

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## *Editorial*

Access to high cost medicines are a problem round the world especially in the low and middle income countries. Low health care budget and absence or low coverage of Health Insurance makes the situation more complex. Respective governments have taken measures for innovations and framed various legislation to make high priced medicines more accessible. India has taken several steps for Universal Health care by introducing new initiatives like- Unorganized Workers Social Security Act (2008), Rashtriya Swasthya Bima Yojana (RSBY), National Rural Health Mission (NRHM), National Urban Health Mission (NUHM) for overall development of the health care system. Several other steps have also been taken to make medicines more accessible like- Pradhan Mantri Jan Aushadhi Scheme. Greater number of drugs, including high priced medicines have been included under the price control mechanism, through which price of the medicines are monitored by the National Pharmaceutical Pricing Authority (NPPA) under the Department of Pharmaceuticals, Government of India. Several state Governments have taken up innovative projects to improve accessibility to high cost medicines. Government of India has also utilized flexibilities of IPR provisions in case of public health care exigencies by granting compulsory licensing making life saving medicines affordable. In the innovation part the Government of India declared the policy "Make in India". Hope this programme will be successful in case of innovation.



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## Over 24,000 Clinical Trial Deaths In India In Ten Years

Pharmaceutical companies conducting clinical trials in India are increasingly taking advantage of the lacunae in the law and regulatory framework, which is resulting in a spurt in cases of "serious adverse events" (SAEs) and deaths of clinical subjects (participants on whom research/clinical trial is done). An RTI response received by NGO Swasthya Adhikar Manch, a copy of which is with *The Sunday Guardian*, reveals that a total of 24,117 cases of deaths and SAEs due to clinical trials occurred between January 2005 and September 2016. The RTI also revealed that out of the 4,534 deaths that have been reported, only 160 cases have received compensations from the pharmaceutical companies.

According to the RTI response, 341 cases of SAEs resulting in death were reported in 2015, out of which only four cases were compensated. In 2014 and 2013, respectively, 443 and 590 cases of SAEs resulting in death were reported, out of which 21 and 45 cases were compensated. In 2016, 252 cases of SAEs resulting in death were reported; the number of cases that has been compensated is still under examination. Other than the numbers, the Drugs Controller General of India (DCGI), in its RTI reply, has not provided any information on the compensations provided.

Researchers, lawyers and health activists that *The Sunday Guardian* spoke to, pointed to a lax clinical trial policy, irregularities in informed consent of the clinical subjects, and a nexus between pharmaceutical companies and doctors for financial gains as the major reasons behind the rise in unregulated trial practices.

For details: <https://www.drugscontrol.org/news-detail.php?newsid=17067>

## Safety News:

## Corticosteroids Rare risk of central serous chorioretinopathy

The MHRA has provided advice to health-care professionals on the risk of central serous chorioretinopathy (CSCR) with local as well as systemic administration of corticosteroids. Corticosteroids are indicated for a wide variety of indications in the treatment or suppression of inflammatory and allergic disorders, commonly including: • asthma and allergic rhinitis • systemic inflammatory disorders, for example, rheumatoid arthritis • skin conditions, for example, eczema CSCR is a rare adverse effect that occurs with all formulations and has been described after local administration of corticosteroids via inhaled and intranasal, epidural, intraarticular, topical dermal and periocular routes. Although blurred vision is a symptom of CSCR, it is also an established adverse effect of steroid treatment. The causes of blurred vision are various and can also include cataract and glaucoma. The MHRA has recommended that patients are provided with guidance to report any vision problems or disturbances. If a patient has received treatment with local administration of a corticosteroid and presents with visual symptoms, referral to an ophthalmologist should be considered.

Reference: Drug Safety Update, MHRA, Volume 11, issue 1: 2, August 2017 ([www.gov.uk/mhra](http://www.gov.uk/mhra))

## Ketamine Risk of severe liver injury with repeated and/or prolonged high-dose use

The ANSM has received reports of serious liver injury potentially related to the repeated and/or prolonged use of high dose ketamine. The ANSM has reminded healthcare professionals that good practice recommendations for use of ketamine should be implemented. It is essential to observe the recommended dosages and monitor the liver function closely. Ketamine is indicated as an

anaesthetic agent, alone or in combination with other anaesthetics. Ten cases of serious liver injuries, including four cases leading to liver transplantation, have been reported by healthcare professionals since 2014. These are cholestatic type cholangitis, which may be linked to the repeated and/or prolonged administration of ketamine.

Reference: Point d'information, ANSM, 20 June 2017, France ([www.ansm.sante.fr](http://www.ansm.sante.fr))

### **Lithium Risk of toxicity**

The TGA has reminded health-care professionals to remain vigilant for potential signs of lithium toxicity, particularly in patients with risk factors. Early symptoms of lithium toxicity can occur close to or within the serum therapeutic range. Lithium (Quilonum® and Lithicarb®), is indicated for the treatment of acute mania, hypomania and for the prophylaxis of manic depressive illness. The risk of lithium toxicity is adequately addressed in the product information for lithium. A patient died in 2013 as a result of lithium toxicity and has prompted this reminder. As of 17 May 2017, the TGA has received 58 reports in which lithium was suspected of causing toxicity. Two of these cases resulted in death. Interactions with other medicines were identified as a contributing factor in 17 cases, and may have played a role in four other cases. Inappropriate dosing was found to be a contributing cause of toxicity in two cases, and may have contributed to a third case.

Reference: Medicines Safety Update, TGA, Vol. 8, No. 4, August/September 2017 ([www.tga.gov.au](http://www.tga.gov.au))

### **Pembrolizumab Risk of using pembrolizumab for multiple myeloma in combination with immunomodulatory agents**

The US FDA has informed the public, health-care professionals and oncology clinical investigators about the risks associated with the use of pembrolizumab (Keytruda®) in combination with dexamethasone and an immunomodulatory agent (lenalidomide or pomalidomide) for the treatment of patients with multiple myeloma.

Pembrolizumab is used for certain types of cancers, but is not approved for treatment of multiple myeloma. The FDA statement is based on a review of data from two clinical trials evaluating the use of pembrolizumab combined with other treatments in patients with multiple myeloma. On 3 July 2017, the FDA required that all patients in these trials should be discontinued from further investigation with this drug because, interim results from both trials demonstrated an increased risk of death for patients receiving pembrolizumab when it was combined with an immunomodulatory agent as compared to the control group. The manufacturer was made aware of the issue through an external data monitoring committee recommendation and suspended the trials to enrolment on 12 June, 2017. Other multiple myeloma clinical trials of pembrolizumab and other combinations are currently undergoing clinical evaluation.

Reference: Drug Safety Communication, US FDA, 31 August 2017 ([www.fda.gov](http://www.fda.gov))

### **Regulatory News:**

#### **Azithromycin Risk of acute generalized exanthematous pustulosis**

The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for azithromycin (Zithromax®) has been updated to include the risk of acute generalized exanthematous pustulosis as a clinically significant adverse reaction. Azithromycin is an antimicrobial used for a number of bacterial infections caused by strains of genus Staphylococcus, Streptococcus, Pneumococcus, Neisseria gonorrhoeae, Moraxella (Branhamella) catarrhalis, Haemophilus influenzae, Legionella pneumophila, Peptostreptococcus, Prevotella, Chlamydia, and Mycoplasma. One case of acute generalised exanthematous pustulosis has been reported in Japan. A causal relationship could not be excluded in this case. In addition, the company core datasheet (CCDS) has been updated.

Reference: Revision of Precautions, MHLW/PMDA, 8 August 2017 ([www.pmda.go.jp/english/](http://www.pmda.go.jp/english/))

### **Doxycycline Risk of fixed drug eruptions**

The Saudi Food and Drug Authority (SFDA) has updated the summary of product characteristics and patient information leaflet for doxycycline to include the risk of fixed drug eruptions (FDE). Doxycycline is a tetracycline broad-spectrum antibiotic with bacteriostatic characteristics. It is used as treatment or prophylaxis against a wide range of susceptible strains of gram-negative and gram-positive bacteria and other microorganisms. The SFDA initiated the investigation based on a signal observed in a published case report examining potential associations between doxycycline and risk of FDE. As a result, the SFDA reviewed the available evidence related to this safety issue including screening of the WHO global database of Individual Case Safety Reports, VigiBase. In addition, a literature review was conducted. The SFDA concluded that the available evidence suggests a probable association between doxycycline and FDE.

Reference: Based on the communication from Saudi Food and Drug Authority, December 2016

### **Paracetamol (modified- or prolonged-release) Modified- or prolonged-release preparations should be suspended from marketing**

The EMA has recommended that modified or prolonged-release paracetamol products should be suspended from the market. This is in view of the risks to patients from the complex way these medicines release paracetamol into the body after an overdose. Paracetamol is a medicine that has been widely used for many years to relieve pain and fever in adults and children. The review of modified-release paracetamol has been carried out by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC evaluated published studies and reports of overdose with these medicines, consulted experts in the management of poisoning and assessed how overdose with paracetamol is managed in the EU and other parts of the world. In many cases, it may not be known whether an overdose of paracetamol involves immediate-release or modified release products, making it difficult to decide what type of management is needed. The committee could not identify a way to minimise the risk to patients, or a feasible and standardised way to adapt the management of paracetamol overdose across the EU to allow for treatment of cases that involve modified-release preparations. It concluded on balance that the risk following overdose with these medicines outweighs the advantage of having a longer-acting preparation.

Reference: News and press releases, EMA, 1 September 2017 ([www.ema.europa.eu](http://www.ema.europa.eu))

## **56<sup>th</sup> National Pharmacy Week Celebration**

19<sup>th</sup> – 26<sup>th</sup> November 2017

Indian Pharmaceutical Association, Bengal Branch

Theme: Know about your medicines: Ask your Pharmacist

Inauguration on 19<sup>th</sup> November:

Venue: Dr. Triguna Sen Auditorium, Jadavpur University, Kolkata

### **Week long Programme**

20.11.2017: Bharat Technology, Uluberia & Blood Donation at IP Jalpaiguri

21.11.2017: Students' Day Programme  
Dr. B.C.Roy College of Pharmacy & Allied Health Sciences, Durgapur

22.11.2017: Institute of Pharmacy Kalyani

23.11.2017: Hospital Pharmacy Day At Bankura  
Sammilani Medical College, Bankura

24.11.2017: Jakir Hossain Institute of Pharmacy,  
Miapur, Murshidabad

25.11.2017: Cultural Programme, IPA Auditorium

26.11.2017: Celebration at Jalpaiguri  
Seminar at DSP, Durgapur

### **DISCLAIMER:**

The Newsletter intends to provide updated and reliable information on medicines and other related issues in an attempt to equip healthcare professionals to take informed decision in recommending medicines to the patients. However, they are encouraged to validate the contents. None of the people associated with the publication of the Newsletter nor the organization shall be responsible for any liability for any damage incurred as a result of use of contents of this publication. The brand names of medicines, if mentioned, are for illustration only and the Newsletter does not endorse them.