Drug Information Bulletin

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Content

Editorial

Schedule H1 has been introduced in the Drugs & Cosmetics Rules vide a notification dated 30th August 2013, which is effective from 1st March 2014, and includes 46 drugs including antibiotics, drugs having potential for misuse etc. Out of 46 drugs, 26 drugs were shifted from Schedule H and 20 more drugs have been included in this schedule.
The main aim was to reduce irrational use of antibiotics, which is a major cause of developing resistance to antibiotics. It was noted that all medicines including antibiotics are available from community pharmacy over the counter in India. Thereafter some more medicines were included in this list as their irrational use created health hazards and social problems.
The sale of these drugs has made regulated imposing additional conditions. Firstly the label of the drugs should bear a warning-

"SCHEDULE H1 DRUG-WARNING
-it is dangerous to take this preparation except in accordance with the medical advice.
-not to be sold without the prescription of a registered medical practitioner"

Label should contain RX symbol in red color at the left top corner. Supply of a drug included in Sch. H1 requires to be recorded in a separate register at the time of supply including the Name & address of the prescriber, Name & address of the patient, Name of the drug and quantity supplied. The record requires be preserving for 3 years and making ready for inspection.
This legislation has taken effect since 1st March 2014, but some problem cropped up during implementation. As a result DCGI has issued a clarification that if a drug manufactured upto 28th February 2014 that may not have required caution in the label, but retailers require to follow the procedure as prescribed in the notification dated 30.08.2013.

Dr. Subhash C. Mandal
Editor

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Courtesy: Pharmatimes

New Drug: Mirabegron

Approved indication: overactive bladder
Betmiga (Astellas)
25 mg and 50 mg film-coated tablets
Australian Medicines Handbook section 13.1

People with overactive bladder have urgency with or without frequency and nocturia. Antimuscarinics such as oxybutynin, tolterodine, solifenacin (Aust Prescr 2006; 29:138-43) and darifenacin are the mainstay of drug treatment (Aust Prescr 2014;37:10-3). They are often used in conjunction with bladder training.

Mirabegron is an agonist of $beta_3$ adrenergic receptors. It works by activating these receptors in the detrusor muscle of the bladder. This relaxes the muscle and increases bladder capacity.

The safety and efficacy of mirabegron has been evaluated in three placebo-controlled, 12-week studies.1-3 A pooled analysis of the trials found that once-daily 50 mg and 100 mg doses statistically improved incontinence and micturition frequency.4 However, there was no dose–response effect. The mean number of incontinence episodes per day fell by 1.48 with mirabegron 50 mg and by 1.54 with the 100 mg dose. Incontinence episodes fell by 1.09 a day with placebo. Although an active control was included in one of the trials (extended-release tolterodine), a statistical comparison with mirabegron was not reported.2

The most common adverse effects with mirabegron and placebo included hypertension (7.3% vs 7.6% of participants), nasopharyngitis (3.4% vs 2.5%), urinary tract infection (3% vs 1.8%), headache (2.9% vs 3.1%), dry mouth (2% vs 2.1%) and constipation (1.6% vs 1.4%).4 Tachycardia was common, occurring in 1.2% of people taking mirabegron 50 mg. Palpitations and atrial fibrillation have also been reported. Blood pressure monitoring is recommended, especially in patients with hypertension, and mirabegron is not recommended in uncontrolled hypertension. Caution is urged in those who may have a prolonged QT interval.

In a long-term extension study of safety (52 weeks), 11 of 820 people who received mirabegron 100 mg had a neoplasm (benign or malignant). Only 1 of 812 people reported a neoplasm with mirabegron 50 mg and 4 of 812 people who received tolterodine.

Following an oral dose, mirabegron reaches peak plasma concentrations after 3–4 hours. Steady-state concentrations are achieved after seven days. The terminal half-life is approximately 50 hours and the drug is eliminated in the urine (55%) and faeces (34%). This drug is not recommended in patients with end-stage renal disease or severe hepatic impairment.

In animal studies, mirabegron has shown reproductive toxicity and is excreted in milk. It is therefore not recommended in pregnancy or lactation.

Mirabegron is transported and metabolised by multiple pathways so there is potential for drug interactions. Monitoring and dose adjustment may be needed with concomitant drugs that are extensively metabolised by CYP2D6 and have a narrow therapeutic index, such as flecainide and imipramine. Mirabegron also increases exposure to concomitant digoxin so digoxin should be started at a low dose and titrated based on serum concentrations.

Mirabegron is indicated for urgency, increased micturition frequency and urgency incontinence in adults with overactive bladder. It showed only modest efficacy in the trials with the average number of incontinence episodes being reduced by around 1.5 a day. This was compared to people given placebo who had approximately 1.1 fewer incontinence episodes a day. Currently, there are limited comparative and long-term efficacy data with this drug. In the UK5, mirabegron is only recommended when antimuscarinic drugs are contraindicated, ineffective or not tolerated.

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Ref. *Aust Prescr 2014; 37:64-71*

Supreme Court wants more clarity on Clinical Trial

The Supreme Court on Monday directed the Union health ministry to make drug companies that want to experiment with new formulations answer three queries in a format to be prepared by the technical committee.

The pharmaceutical companies must specify whether the risk involved in testing the new formulations on human beings is justified by the benefits expected from the exercise, whether there are unmet needs for the drug in this country necessitating the innovation and whether safer are methods available.

The court stated that by demanding responses on these three parameters, a lot of confusion can be obviated. The Bench headed by Justice R M Lodha gave two months' time to the government to follow the order.

The order was passed in the public interest petition moved by Swasthya Adhikar Manch alleging deaths and injuries to poor people in Madhya Pradesh, where unmonitored experiments were allegedly organised on without getting informed consent from the subjects.

Counsel Sanjay Parikh mentioned a news report in which it was alleged that 254 persons died in 15 years in US-funded

clinical trials conducted on a control group without screening.

While the government objected to mentions of news reports, the court allowed Parikh to file an application including the report, which will be considered in the next hearing.

When Parikh alleged that neither the government nor the sponsors gave compensation for the deaths and permanent injuries, the judges suggested that the compensation could be paid first by the government and it could be recovered from the companies. Victims could be informed about compensation rights through ads or opening an office where they can record their claims.

Parikh argued that in the past few years, there were 125 deaths resulting from experiments with one chemical alone and compensation was given only for five deaths. Adequate information regarding compensation to the death and injury cases was not coming forth and there were inconsistencies in what the government stated in the court and what was available from right to information queries.

Additional Solicitor- General Siddharth Luthra said committees have been constituted to look into the claims for compensation. When it was pointed out that years have gone by without any decision, the counsel explained that the government had to see whether the victims have already availed of insurance benefits and assess the actual degree of damage suffered in each case.

He said those who suffered injuries are given treatment. The judges observed that sometimes deaths would be preferred then continue with the suffering.

Drug-resistant superbugs now a global threat

The World Health Organization has announced in a report that antibiotic resistance is now a major threat to public health worldwide. The agency reports that several types of bacteria, such as methicillin-resistant Staphylococcus aureus, K. pneumoniae and E. coli, have mutated to develop immunity to drugs such as carbapenems and fluoroquinolone and cause diseases such as pneumonia, bloodstream infections, urinary tract infections and gonorrhea. Keiji Fukuda, assistant director-general for health security at WHO, stressed the need for a renewed approach on the use of antibiotics to prevent infections and defeat drug resistance.

Ref. The Economist

Five most recall-Prone Medical Devices

First there were issues with leaking, low-voltage batteries. Then it was a pressure sensor calibration drift.

The sad thing is that Hospira actually wasn't alone when it came to its GemStar Infusion System being involved in multiple serious recalls.

Look at the five devices garnering the most Class I recall designations from the FDA since the start of 2012, and two involved infusion systems including Gemstar. Another two involved implanted drug infusion pumps. It is little wonder that the FDA considers infusion pumps to be a high-recall area in need of more attention. And when multiple types of problems are found with a single device, questions arise whether there were systemic issues behind the way companies were guaranteeing manufacturing quality for device components. It is a growing challenge for many medical device manufacturers as supply networks become increasingly complex and outsourced.