Drug Information Bulletin

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Content

Editorial

Heat stable Carbetocin-an equivalent of Oxytocin is in the offing!

A recent clinical trial report published in *The* new england journal *of* medicine concluded that heat-stable Carbetocin is noninferior to Oxytocin for the prevention of blood loss of at least 500 ml or the use of additional uterotonic agents. Carbetocin does not require refrigeration as it is stable at 30 degree celcius. A single dose of 100 mcg /ml of Carbetocin is administered by bolus injection, slowly over 1 min.

An international, randomized, double-blind, active-controlled, noninferiority trial comparing heat-stable carbetocin with oxytocin for the prevention of postpartum hemorrhage during the third stage of labor in women giving birth vaginally at 23 hospitals (sites) in 10 countries — Argentina, Egypt, India, Kenya, Nigeria, Singapore, South Africa, Thailand, Uganda, and the United Kingdom — between July 7, 2015, and January 30, 2018 was conducted by the WHO, Ferring Pharmaceuticals, and Merck.

In India Oxytocin is misused for more milk and fast growing of vegetables. Considering this problem, the Ministry of Health and Family Welfare has restricted the manufacture of Oxytocin formulations for domestic use to public sector only from 1st July 2018. It has also banned the import of Oxytocin and its formulations. From 1st July 2018, no private manufacturer will be allowed to manufacture the drug for domestic use. The effective date was further deferred by 120 days through a notification vide S.O. 3448 (E) dtd. 13th July 2018. Hope these measures will evoke good results

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Drug Safety:

Antimalarial drugs: Risk of Stevens Johnson syndrome (SJS).

NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for the artesunate combination antimalarial drug (artemether and lumefantrine) is revised to include the risk of Stevens Johnson syndrome. Artemether-lumefantrine are used in combination for the treatment of uncomplicated malaria. Between July 2011 and March 2018, NCC-PvPI received four ICSRs of SJS with artemether and lumefantrine use. The cases were reviewed by SRP-PvPI, IPC, and a strong causal relationship between artemether, lumefantrine and SJS was suggested.

Reference: Based on the communication from IPC, NCC-PvPI, India (http://ipc.nic.in)

Amlodipine: Risk of Alopecia.

The National Coordination Centre - Pharmacovigilance Programme of India (NCC-PvPI), Indian Pharmacopeia Commission (IPC) has made a recommendation to the Central Drugs Standard Control Organisation (CDSCO) requesting that the drug safety label for amlodipine is revised to include alopecia as an adverse drug reaction. Amlodipine is used for the treatment of angina, hypertension and coronary artery disease. Between July 2011 and August 2017, NCCPvPI received seven individual case safety reports (ICSRs) of alopecia with amlodipine use. The cases were reviewed by Signal Review Panel (SRP)- PvPI, IPC and they showed a strong causal relationship between amlodipine and alopecia.

Reference: Based on the communication from IPC, NCC-PvPI, India (http://ipc.nic.in)

Amlodipine: Risk of Gingival Hypertrophy.

NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for amlodipine is revised to include gingival hypertrophy as an adverse drug reaction. Between July 2011 and March 2018, NCC-PvPI received 44 ICSRs reporting gingival hypertrophy with amlodipine use. The cases were reviewed by the Signal Review Panel (SRP)-PvPI, IPC and they suggested a strong causal relationship between amlodipine and gingival hypertrophy. Reference: Based on the communication from IPC, NCC-PvPI, India (http://ipc.nic.in)

Carbamazepine Risk of DRESS India.

NCC-PvPI, IPC has made a recommendation to the CDSCO about the revision of the drug safety label for carbamazepine to include DRESS. Carbamazepine is used for the treatment of partial seizures with or without secondary generalisation; trigeminal neuralgia; and bipolar disorder. Between July 2011 and March 2018, NCC-PvPI received 33 ICSRs of DRESS syndrome associated with carbamazepine use. The cases were reviewed by the Signal Review Panel (SRP)-PvPI, IPC who found a strong causal relationship between carbamazepine and DRESS syndrome.

Reference: Based on the communication from IPC, NCC-PvPI, India (http://ipc.nic.in) (See WHO Pharmaceuticals Newsletters No.1, 2017: HLA-B 1502 genotyping to minimize carbamazepine-induced severe cutaneous adverse reactions in Singapore; No.2, 2016: Risk of Stevens Johnson's Syndrome in India; No.1, 2013: Potential risk of serious skin reactions associated with the HLA-A 3101 allele in UK)

FDCs expose patients to many risks such as dosing mismatch, toxicity: Expert Panel

While recommending continuation of the ban on 300-plus fixed dose combination (FDC) drugs, the expert sub-committee of the Drugs Technical Advisory Board (DTAB) has made it clear that the use of these "irrational" drug cocktails will expose patients to unnecessary overuse risks and dosing mismatch in these products can result in toxicity. The panel constituted to review the ban on 349 FDCs - drugs containing two or more active pharmaceutical ingredients in a fixed dosage ratio - has recommended that 343 of them should be "prohibited" and the remaining six need to be "restricted or regulated".

The fate of these combination drugs will now be decided by the government. The panel report is expected to reach the health ministry in the coming days. A decision to keep the ban is expected to deal a severe blow to the pharmaceutical industry as it affects as many as 6,000 brands from top manufacturers.

The sub-committee report is seen as a huge victory for public health activists and patient

advocacy groups who have been fighting to root out these risky drug combinations. The health ministry banned these medications after a committee headed by Prof CK Kokate declared them unsafe. Drug makers challenged the ban in high courts across the country. In January this year, the ministry moved the apex court challenging a Delhi high court order that quashed the ban. The DTAB panel was constituted in accordance with the top court's order to re-examine the issue.

Aidan, a consortium of non-profits in the health sector, had also filed a petition in the top court against the Delhi high court order.

According to official documents reviewed by Pharmabiz, the expert sub-committee has noted in its report that three FDCs should be "restricted for specific indications or diseases" and the other three should be "restricted to specific quantities of ingredients and for specific indications".

The documents show that the panel has made some stern observations on the claims of FDC manufacturers. The published literature provided by these companies to justify the FDCs "were not relevant (epidemiological data not from India), relied on a few biased studies, indications mentioned were too broad/absurd/vague and were not as per treatment guidelines", it stated.

For most FDCs, "their use would lead to unnecessary overuse and the patients would be exposed to the risk of multiple ingredients when one would suffice". In FDCs where there is dosing mismatch, its "use will result in toxicity wherein the ingredient is being administered more frequently than required, or lack of effect wherein the ingredient has been administered less frequently than required. An inability to adjust doses of individual ingredients is especially risky if an ingredient has a narrow safety margin", the panel observed in its report.

"Appellants claimed safety by quoting OTC (over the counter) products in UK and US markets, ignoring the lacunae in the OTC system, label requirements of OTC products (eg. not for children under 12 years of age), lack of efficacy and withdrawal by innovator of some products. Some appellants wished to change indication and/or carry out studies in support of their respective FDCs. They were advised to follow D&C Act for new drugs," the committee further stated.

The report has sent shockwaves through the pharmaceutical industry. "It is going to severely affect us. At one end, the surging cost of raw materials and packaging items is taking a heavy toll on production. Moreover, there is acute shortage of APIs and their prices have skyrocketed. In the coming months we are anticipating closure of many manufacturing units," Bihar Drugs and Pharmaceutical Manufacturers' Association president Sanjiv Rai said.

The DTAB panel was headed by Dr Nilima Kshirsagar, the chair in clinical pharmacology at ICMR Mumbai. The panel and co-opted experts held 41 meetings and reviewed 812 representations from appellants including Aidan and hearing from 467 companies for 156 FDCs. It also relied on literature in scientific peer-reviewed journals, meta-analysis by international organisations and guidelines issued by the World Health Organisation.

Source: Pharmabiz

US FDA approves tafenoquine for the radical cure of P. vivax malaria

First single-dose medicine to prevent the relapse of P. vivax malaria marks a major contribution towards malaria eradication efforts. GSK and Medicines for Malaria Venture (MMV) today announced that the United States Food and Drug Administration (FDA) has approved, under Priority Review, single-dose Krintafel(tafenoquine) for the radical cure (prevention of relapse) of Plasmodium vivax (P. vivax) malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute P. vivax infection.

Dr. Hal Barron, Chief Scientific Officer and President of Research and Development, GSK, said: "Today's approval of Krintafel, the first new treatment for Plasmodium vivax malaria in over 60 years, is a significant milestone for people living with this type of relapsing malaria. Together with our partner, Medicines for Malaria Venture, we believe Krintafel will be an important medicine for patients with malaria and contribute to the ongoing effort to eradicate this disease."

Dr. David Reddy, Chief Executive Officer of MMV said: "The US FDA's approval of Krintafel is a major milestone and a significant contribution towards global efforts to eradicate malaria. The world has waited decades for a new medicine to counter P. vivax malaria relapse. Today, we can say the wait is over. Moreover, as the first ever single-dose for this indication, Krintafel will help improve patient compliance. We are proud to have worked side-by-side with GSK for more than a decade to reach this point. Our focus is now on working to ensure the medicine reaches the vulnerable patients that need it most."

The approval was based on efficacy and safety data from a comprehensive global clinical development P. vivaxradical cure programme designed in agreement with the FDA. Thirteen studies in healthy volunteers and patients directly supported the programme. The primary evidence for the clinical efficacy and safety of the 300mg single-dose, to which more than 800 subjects were exposed, was provided by three randomised, double-blind studies: DETECTIVE Part 1 and Part 2 (TAF112582) and GATHER (TAF116564). The results of the two phase III studies were announced in June 2017. The submission included data analysed from a total of thirty-three studies involving more than 4,000 trial subjects exposed to the 300mg single-dose and other doses of tafenoquine.

With the approval of Krintafel, the FDA awarded GSK a tropical disease priority review voucher. The tropical disease priority review voucher programme is designed to encourage development of new drugs and biological products for prevention and treatment of certain neglected tropical diseases affecting millions of people throughout the world.

The new drug application (NDA) was submitted by GSK to the FDA in November 2017 and a regulatory submission was also made to the Australian Therapeutics Good Administration (TGA) in December 2017. A decision from the TGA is awaited. Approvals by FDA and TGA will be informative to other regulatory agencies for their own approval process in malaria-endemic countries where tafenoquine will be provided as a not-for-profit medicine to maximise access to those who need it most.

For details: https://www.mmv.org/newsroom/

Forthcoming Events:

- **27th FAPA Congress**
  October 24th-27th, 2018
  Manila, Philipines
- **57th National Pharmacy Week(NPW)**
  18-24th November 2018
  Theme: Pharmacists for a Healthy India
- **70th Indian Pharmaceutical Congress (IPC)**
  21-23 Dec 2018
  Amity University, Noida, NCR Delhi

78th FIP World Congress of Pharmacy and Pharmaceutical Sciences

2 - 6 September 2018 Glasgow, UK