



Drug Information Bulletin

Drug Information Centre (DIC)

Indian Pharmaceutical Association

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Editorial

Recently Pharmacovigilance Programme of India (PvPi) has issued an advisory not to use Nimesulide below 12 years children following an incident of developing Steven's Johnson syndrome, a rare and serious disorder of skin and mucous membrane in a 10 year boy as a result of administration of 100 mg Nimesulide Tablet for one day. This incident is an eye opener to the prescriber, who are inappropriately prescribing Nimesulide for the treatment of fever inspite of banning of use of Nimesulide use below 12 years by the Government of India in the year of 2011 vide notification G.S.R. 82(E) dated February 10, 2011.

It may be noted that this drug is not approved by some of the developed country, still it is available in India.

A section of manufacturers of Nimesulide formulation is also pushing it for pediatric use by several means utilizing loopholes of the regulatory system.

This incident has given strong message to all stake holders to be serious in discharging their duties-

1. Manufacturers: Follow the rules and do not adopt unfair means to promote the formulation.
2. Prescribers: Be cautious in case of prescribing medicines, which may harm your patients.
3. Pharmacists: Before dispensing be sure it will not harm your patient. If you feel so, please consult prescriber.

Hope all healthcare providers will be serious in their duties for the safety of the patients.



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Tramadol Potential risk of hiccups

The NCC-PvPI, IPC has made a recommendation requesting that the PIL for tramadol is revised to incorporate hiccups as a potential adverse drug reaction. Tramadol is used for the treatment of mild to moderate pain. Between July 2011 and December 2018, NCC-PvPI received six ICSRs reporting hiccups associated with the use of tramadol. NCC-PvPI also assessed 83 ICSRs reporting this drug-ADR combination in the WHO global database for reports of adverse events. The cases were reviewed by the SRP-PvPI, IPC, and the information in the cases suggested a strong causal relationship between tramadol and hiccups.

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

Glibenclamide Risk of palpitations

The NCC-PvPI, IPC has advised CDSCO to request the revision of the PIL for glibenclamide to include palpitations as an adverse drug reaction. Glibenclamide is used for the treatment of diabetes mellitus. Between July 2011 and December 2018, NCC-PvPI received 12 ICSRs of glibenclamide associated palpitation. The NCC-PvPI also assessed 103 relevant reports from the WHO global database for reports of adverse events and the literature. A signal was published by the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, UMC) which identified this reaction as a signal in the Asian population. The cases were reviewed by SRP at the NCC-PvPI, IPC, and a strong causal relationship between glibenclamide and palpitations was suggested.

Paracetamol Dangerous when not used correctly

Medsafe has announced that they have received cases of serious adverse events related to medication errors associated with prescribing, dispensing and communication to caregivers in children. Paracetamol, also known as acetaminophen, is generally indicated to treat mild to moderate pain relief. The Medicines Adverse Reactions Committee (MARC) discussed a report of acute hepatic failure in a child given a suspected paracetamol overdose. Following a review of the cases, advice on actions to take when prescribing and dispensing paracetamol for children were provided. For example, paracetamol should be used only for approved indications (pain, fever). The correct dose should be calculated using body weight. Health-care

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

Statin use tied to increased diabetes risk, study finds

Researchers studied 9,535 people without diabetes, ages 45 or older, and found that those who took statins had higher insulin resistance and blood glucose levels after 15 years, and they were 38% more likely to develop type 2 diabetes, compared with those who did not take the drugs. The findings in the [British Journal of Clinical Pharmacology](#) revealed an even greater risk among those who had an impaired glucose balance and were overweight or obese.

Ref. [Diabetes \(UK\)](#)

FDA establishes center of excellence for compounded drugs

The FDA said it has established a Compounding Quality Center of Excellence to improve the quality and safety of compounded medications by offering educational programs and other learning tools to outsourcing facilities. "While engagement is voluntary, this initiative will provide an increased awareness and understanding of common issues and provide innovative ways to address challenges outsourcing facilities may face," according to Center for Drug Evaluation and Research Director Janet Woodcock.

Ref. [European Pharmaceutical Review \(UK\)](#)

professionals should prescribe paracetamol precisely and dispense diligently.

Reference: Prescriber Update, Medsafe, September 2019

Tramadol Possible risk of opioid effects in breastfed babies

Medsafe has announced that CARM received a case report where a neonate suffered feeding disorder, somnolence (sleepiness), respiratory disorder and weight decrease while the breastfeeding mother was taking tramadol (Tramal® and Arrow®). Tramadol is indicated for the relief of moderate to severe pain and is used to help manage pain after a caesarean section. Small amounts of tramadol and its metabolite, which also helps with pain, are found in breast milk when taken by the mother. Although the

amounts of tramadol and its metabolite are too low to cause a problem, there is a risk that the baby's breathing may be affected or that the baby may be allergic to tramadol or its metabolite. Medsafe will continue to monitor this issue and will produce updated advice for health-care professionals and consumers as necessary. Reference: Safety Communications, Medsafe, 9 August 2019 (www.medsafe.govt.nz/) (See WHO Pharmaceuticals Newsletter No.4, 2019: Contraindication in children: Risk of serious respiratory depression in Japan; No.1, 2018: Limited use: Only for adults of 18 years of age and older in USA)

Vildagliptin Risk of hepatotoxicity

Medsafe has announced that hepatotoxicity is the most significant risk of harm with vildagliptin. Vildagliptin is a potent and selective dipeptidyl-peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes. Medsafe encourages healthcare professionals to perform liver function tests before starting and stopping treatment. Also, the use of vildagliptin should be avoided during pregnancy unless the expected benefits outweigh any potential risks. The CARM received 15 reports where vildagliptin was suspected. The 15 reports describe 36 reactions, including hepatic reactions, oedema, cardiac disorders, mood disorders and gastrointestinal disorders.

Reference: Prescriber Update, Medsafe, September 2019 (www.medsafe.govt.nz/)

New Drug: Neratinib for breast cancer

Nerlynx (Specialised Therapeutics)

40 mg film-coated tablets

Neratinib is indicated for extended adjuvant treatment in women with early-stage HER2-positive breast cancer following adjuvant trastuzumab-based chemotherapy. It should be started within a year of finishing trastuzumab. Neratinib is a tyrosine kinase inhibitor. It irreversibly binds to the HER1, HER2 and HER4 receptors. This binding reduces auto-phosphorylation and downstream signalling from these receptors and decreases growth of the cells.

The approval of neratinib is based on a placebo-controlled phase III trial of 2840 women who

had stage I–III HER2-positive breast cancer.^{1,2} Most participants had completed their last trastuzumab dose within a year of starting the trial. Women were randomised 1:1 to receive neratinib (240 mg/day) or placebo for 12 months. The primary outcome of the trial was invasive disease-free survival, which included invasive ipsilateral tumour recurrence, invasive contralateral breast cancer, local or regional recurrence, distant recurrence or death from any cause.

In two-year and five-year analyses, invasive disease-free survival rates were statistically higher with neratinib than with placebo (93.9% vs 91.6% at 2 years and 90.2% vs 87.7% at 5 years). However, there was no statistically significant difference between the neratinib and placebo groups for other outcomes including distant disease-free survival and CNS recurrence.^{1,2} In a subgroup analysis of invasive disease-free survival at five years, women who had completed their last trastuzumab dose more than 12 months before starting the trial gained no benefit from neratinib (hazard ratio=1).²

The most common adverse events with neratinib included diarrhoea (93.6%), nausea (42.5%), fatigue (27.3%), vomiting (26.8%), abdominal pain (22.7%), rash (15.4%), decreased appetite (13.7%), stomatitis (11.2%) and muscle spasm (10%). Diarrhoea was severe (grade 3) in 40% of cases,¹ and 14.4% of women discontinued because of it. Loperamide prophylaxis (along with adequate hydration) is therefore recommended for the first 1–2 months of treatment, and as needed after that. The neratinib dose may need to be reduced, interrupted or discontinued depending on the severity of the diarrhoea.

Women with renal impairment have a higher risk of complications from dehydration with diarrhoea and should be closely monitored. Neratinib is not recommended in severe renal impairment or dialysis.

Liver toxicity was more common with neratinib than with placebo (12.4% vs 6.6%) and included elevated alanine aminotransferase, aspartate aminotransferase and blood alkaline phosphatase. The dose may need to be reduced or discontinued depending on the severity of the

hepatotoxicity. Neratinib is contraindicated in severe hepatic impairment (Child-Pugh C).

The recommended dose of neratinib is 240 mg once daily for a year. Tablets should be taken in the morning with food. Following oral administration, peak plasma concentrations are reached after seven hours. Neratinib is extensively metabolised in the liver, primarily by cytochrome P450 (CYP) 3A4. Its plasma half-life is 17 hours and most of the dose is excreted in the faeces.

Neratinib has numerous drug interactions. Concomitant use of strong CYP3A4 and P-glycoprotein inducers should be avoided (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin and St John's wort). CYP3A4 inhibitors (fluconazole, diltiazem, verapamil, erythromycin) should also not be co-administered. If CYP3A4 inducers or inhibitors cannot be avoided, the neratinib dose should be increased or decreased accordingly (see product information).

Neratinib's solubility goes down with increasing pH, so some drugs may affect its bioavailability. Concomitant proton pump inhibitors should be avoided and neratinib should be given separately from H₂-receptor antagonists and antacids.

As there was evidence of fetal toxicity in animal studies, women should use contraception during and for one month after finishing neratinib treatment. It is unclear if the drug reduces the

effectiveness of hormone contraceptives so women should add a barrier method. It is not known if neratinib is excreted in breast milk.

Neratinib improved the invasive-free 5-year survival rate of women with HER2-positive breast cancer by 2.5% compared to placebo. Those with hormone-receptor positive breast cancer seemed to have more benefit than those without the receptor. It is currently unclear whether improved invasive-free survival will lead to improved overall survival. The modest benefits of neratinib have to be weighed against the very high likelihood of diarrhoea, which was severe in 40% of women who were treated.

References

1. Chan A, Delaloge S, Holmes FA, Moy B, Iwata H, Harvey VJ, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre randomised double-blind placebo-controlled phase 3 trial. *Lancet Oncol* 2016;17:367-77.
2. Martin M, Holmes FA, Ejlertsen B, Delaloge S, Moy B, Iwata H, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised double-blind placebo-controlled phase 3 trial. *Lancet Oncol* 2017; 18:1688-700.

Ref. Australian Prescriber

Annual Get together of IPA, Bengal Branch

Venue: Dhamakhali Zila Parishad Picnic spot

Date: 19.01.2020

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Health Camp organized by IPA, Bengal Branch at Gangasagar. West Bengal

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