Drug Information Bulletin

Drug Information Centre (DIC)

Indian Pharmaceutical Association

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Content

Editorial

The year 2015 has started remarkably with several developments in the health care system of India. The Department of Health and Family Welfare proposes to introduce the Drug and Cosmetics (Amendment) Bill, 2015 in the Budget Session of the Parliament. The said is placed in public domain (http://www.mohfw.nic.in/) with a view to elicit the comments/views of the stakeholders including the general public. The comments/views may be forwarded to Dr. Shailendra Kumar, Director (Drugs), Department of Health and Family Welfare, Room No-301 'D' Wing, 3rd Floor, Nirman Bhawan, New Delhi-110011 or emailed at anita.tripathi76@nic.in latest by ***January 12, 2015.***

Government of India has appointed a committee for giving recommendation for amendment of Drugs and Cosmetics Rules 1945 to make it contemporary. It has also invited suggestions from association concerned with Drugs, Cosmetics and Medical Devices industry and trade vide a notification dated 24th December 2014. Suggestion / inputs should reach at anita.tripathi76@nic.in latest by ***January 15, 2015.***

Another development is that a draft National Health Policy 2015 has also been published and hosted at http://www.mohfw.nic.in/ for comments, which should be provided online before ***28th February 2015****. This is a golden opportunity for the pharmacists to give inputs for proper utilization of the large pool of pharmacists in the national health care system. Hope all Pharmaceutical organizations will take this opportunity providing their suggestions / inputs in all three matters.*

Dr. Subhash C. Mandal
Editor

New Drug: Crizotinib

Approved indication: non-small cell lung cancer

Xalkori (Pfizer)

200 mg and 250 mg capsules

Australian Medicines Handbook section 14.2.3

Along with erlotinib (Aust Prescr 2006;29:53-5) and gefitinib (Aust Prescr 2003;26:94-5), crizotinib is an oral tyrosine kinase inhibitor for non-small cell lung cancer – it is indicated for people with anaplastic lymphoma kinase (ALK)-positive advanced disease. Rearrangements in this gene lead to continuous activation of the kinase which promotes cell proliferation and inhibits apoptosis. Up to 5% of people with non-small cell lung cancer will have mutated ALK. These are mainly adenocarcinomas and are more likely to occur in non-smokers.

Following an oral dose, peak concentrations are reached after 4–6 hours. Steady state is reached after 15 days with twice-daily dosing. After extensive metabolism in the liver, most of the dose is eliminated in the faeces (63%) and urine (22%). The terminal half-life is 42 hours. Drug concentrations are likely to increase in hepatic impairment so caution is urged in these patients. Dose reduction is needed in people with severe renal impairment (creatinine clearance <30 mL/min).

After showing antitumour activity in two single-arm trials1,2, a phase III trial compared oral crizotinib to intravenous chemotherapy. Patients with locally advanced or metastatic ALK-positive disease despite platinum-based chemotherapy were enrolled. More people responded to crizotinib than to chemotherapy and progression-free survival was significantly longer (see Table). This trend was not reflected in overall survival time which was slightly shorter in people receiving crizotinib. However, people in the chemotherapy group were allowed to cross over to the crizotinib group once their disease progressed.3

The most common adverse events with crizotinib were vision disturbances (60% of patients), diarrhoea (60%), nausea (55%), vomiting (47%), constipation (42%), oedema (31%), fatigue (27%), upper respiratory tract infection (26%), dysgeusia (26%), dizziness (22%), neuropathy (19%), dyspnoea (13%), rash (9%) and alopecia (8%).3 Some patients with vision problems had to have their dose reduced or interrupted.

Hepatotoxicity and interstitial lung disease have occurred with this drug, often in the first two months of treatment. In the phase III trial, 16% of patients had severe elevations in liver enzymes (grade 3 or 4). Two patients had to stop treatment and one patient died of hepatic failure.3 Liver function should be monitored every month and dose reduction is recommended if elevations occur. Two patients taking crizotinib died from interstitial lung disease/pneumonitis.3 Treatment should be discontinued permanently if symptoms develop.

QTc prolongation has been observed with crizotinib and ECG monitoring should be considered in patients who have or may develop a prolonged QT interval. Symptomatic bradycardia can also develop after several weeks of treatment so pulse and blood pressure should be measured each month. Avoid using crizotinib with drugs that slow the heart rate, including beta blockers, verapamil, diltiazem or digoxin. Crizotinib may need to be permanently stopped if severe QTc prolongation or severe bradycardia occur.

Severe neutropenia (13% of patients) and leucopenia (5% of patients) occurred with crizotinib.3 White blood cell counts should be measured and dose reduction or interruption is recommended if these abnormalities occur.

Crizotinib is a substrate and a moderate inhibitor of cytochrome (CYP) P450 3A4/5 so has numerous potential drug interactions. Concomitant use of strong CYP3A inhibitors (some protease inhibitors and azole antifungals, grapefruit juice) or inducers (carbamazepine, rifampicin and St John's wort) may affect plasma concentrations of crizotinib and should be avoided.

Co-administration of drugs with a narrow therapeutic index that are mainly metabolised by CYP3A4 (including cyclosporin, fentanyl and sirolimus) is not recommended. Also avoid CYP3A substrates with a narrow therapeutic index and the potential to cause fatal arrhythmias (dihydroergotamine, ergotamine).

Crizotinib seems to significantly prolong progression-free survival in patients with non-small cell lung cancer, but its effect on overall survival is unclear. Confirmation that a patient has ALK-positive disease is needed before treatment can start. Prescribers and patients should be aware of the life-threatening adverse events that can occur with this treatment.
Efficacy of crizotinib in a comparative phase III trial

References:

1. Camidge DR, Bang Y-J, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 2012;13:1011-8.
2. Crino LL, Kim D, Riely GJ, Janne PA, Blackhall FH, Camidge DR, et al. Initial phase II results with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC): PROFILE 1005 [conference abstract]. J Clin Oncol 2011;29 (Suppl, abstr 7514).
3. Shaw AT, Kim D-W, Nakagawa K, Seto T, Crino L, Ahn M-J, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385-94.

Source: Aust Prescr 2014;37:100-7

Continuing Professional Development: New feature in Australian Prescriber

Australian Prescriber provides Continuing Professional Development (CPD) activities for pharmacists. This means that pharmacists can claim CPD points by testing what they learn from reading articles published in *Australian Prescriber*.

Activities are designed to take about one hour to complete – reading an article and completing an online quiz – and can be included in a pharmacist's CPD plan for two Group 2 non-accredited CPD credits.

To learn more or to participate in the latest activity, visit:
www.australianprescriber.com/continuingprofessionaldevelopment

Rule 122DAB & Schedule Y of the Drugs & Cosmetic Rules amended vide GSR. 889 (E) dated 12th December 2014

Several provisions related to compensation, Responsibilities of Sponsor, Responsibilities of Investigator (s) have been amended by the above mentioned Notification, which is available at http://www.cdsco.nic.in/

A committee has been set up by Government of India for examining and recommending amendments in the Drugs and Cosmetics Rules 1945

Ministry of Health & Family Welfare, Govt. of India has set a committee for examining and recommending amendments in the Drugs and Cosmetics Rules 1945. The said notification also invited inputs from all associations concerned with pharmaceuticals, cosmetics and medical devices industry and trade before 15.01.2015.

OTC Liability for Pharmacists in US

Recently an interesting article published in US Pharm. Regarding the responsibility of a pharmacist in dispensing OTC medicines in US, which is available at http://www.uspharmacist.com

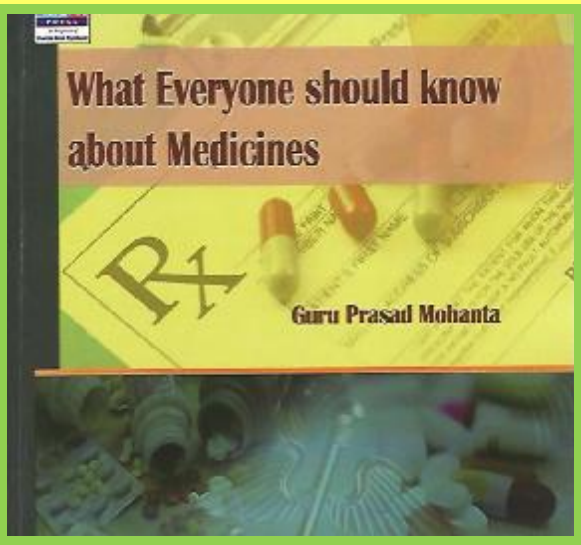
Ondansetron, Tramadol Drug Interaction Identified

In the early postoperative period, Ondansetron is associated with increased requirements for Tramadol consumption, according to a review and meta-analysis published online December 10 in *Anaesthesia*.

Details are available at:

http://www.empr.com/ondansetron-tramadol-drug-interaction-identified/article/389055/

Review:



What Everyone should know about Medicines
Author: Guru Prasad Mohanta
Publisher: PharmaMed Press
Price: INR 250

The author started his book with "Medicines are the greatest weapons of the mankind to fight diseases and death, but are double edged weapons" in the preface. After finishing the book, the readers will feel that the author has deep understanding about the problems of misinformation about medicines and that will be satisfied with the wide range of information the author has provided.

The 300 page book is mainly a compilation of different articles published by the author in different News Papers and Journals within a span of few years. It also includes some more chapters which were not published earlier.

The book contain 67 chapters which covers almost all aspects of Medicines- Its nature, varieties, its use/Misuse, advantages & disadvantages of New drugs, regulation of drugs, Herbal medicines etc.

Lay out and print quality of the book is also good.

The book will definitely satisfy any person interested about medicines.

Dr. Subhash C. Mandal
Editor, DIB