# Drug Information Bulletin

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## Editorial

Recent notification of Pharmacy Practice Regulation 2015 is a landmark in the history of Pharmaceutical Profession in India, which will certainly help in giving proper shape to the unorganized state of Pharmacy Practice in India. In the present regulation the Pharmacy Practice is well defined and the same has set up certain regulation to regulate the same. The document is available at http://www.pci.nic.in/Circulars/Pharmacy%20Practice%20Regulations.pdf .

Some of our professional demands have got legal approval through this regulation, which are-

1. Pharmacists are require to submit Code of Pharmaceutical Ethics and Pharmacists oath with signature for registration
2. Now "Dispensing" is well defined, which will help to ensure dispensing of medicines through Pharmacists
3. Refresher course is mandatory for renewal of registration
4. Pharmacists can charge for his service, in certain cases
5. Name qualification & photograph of pharmacist shall be displayed at a prominent place of the premises
6. Pharmacist require to comply with a dress code……..clean white overall with a badge displaying the name and registration number.
7. This regulation has given a structure of pharmacy cadres in different settings especially in case of hospital pharmacy, which will help in career growth
8. Punishment is well defined for misconduct by Pharmacists

It is felt that the Drugs and Cosmetics Act & Rule require to be amended suitably for proper implementation of this regulation. In spite of such a comprehensive regulation in place there are apprehensions from different quarters about proper implementation of the said regulation. We hope consorted efforts of all professional organizations will help in implementation of this regulation and giving a proper shape to the profession.

***Dr. Subhash C. Mandal***
*Editor*

## New Drugs: Ibrutinib

Approved indication: chronic lymphocytic leukaemia, mantle-cell lymphoma

Imbruvica (Janssen-Cilag)

140 mg tablets

Australian Medicines Handbook section 14.2.3

Ibrutinib is an oral small-molecule drug for B-cell malignancies. It works by binding to Bruton's tyrosine kinase and blocking signalling through the B-cell receptor and cytokine receptor pathways. This inhibits the proliferation of B cells.

Ibrutinib has been registered for the following indications:

- first line for chronic lymphocytic leukaemia in patients with the 17p deletion
- second line for chronic lymphocytic leukaemia and small lymphocytic lymphoma (after at least one previous therapy)
- second line for mantle-cell lymphoma (after at least one previous therapy).

Ibrutinib should be taken once a day. The recommended daily dose is 420 mg for chronic lymphocytic leukaemia and small lymphocytic lymphoma, and 560 mg for mantle-cell lymphoma.

The safety and efficacy of ibrutinib were assessed in several trials.1-3 In general, patients were heavily pre-treated (2–4 previous therapies) and their median ages were 66–68 years. Patients taking warfarin were excluded.

Chronic lymphocytic leukaemia and small lymphocytic lymphoma

The approval is based on a single-arm phase II trial1 and a comparative phase III trial with ofatumumab.2 Most enrolled patients had chronic lymphocytic leukaemia with only 5% having small lymphocytic lymphoma. Approximately a third of those in each trial had an abnormal chromosome 17 (17p deletion), which is associated with a poorer prognosis.

Patients were given daily ibrutinib until their disease progressed or they developed unacceptable adverse effects. In the phase II trial, patients were given 420 mg or 840 mg. Overall, 71% of patients responded to treatment. These were mainly partial responses. At 26 months, the progression-free survival rate was estimated at 75% and overall survival was 83%.

In the phase III trial, ibrutinib 420 mg significantly improved rates of progression-free survival, overall survival and treatment responses compared to ofatumumab.2 The efficacy of ibrutinib was similar in patients with and without the 17p deletion.1,2

Mantle-cell lymphoma

The approval of daily ibrutinib 560 mg for mantle-cell lymphoma is based on an open-label, uncontrolled phase II trial of 111 patients with relapsed or refractory disease.3 Over two-thirds of patients responded to ibrutinib – 23 patients had a complete response and 35 had a partial response. The response rate seemed to be independent of age, previous bortezomib exposure and prognosis at baseline. The estimated median duration of response was 17.5 months and the estimated median progression-free survival was just under 14 months.

Adverse effects and precautions

In a cohort of 357 patients, 6% discontinued treatment because of an adverse event (including infection and subdural haematoma). The most common adverse events were diarrhoea, musculoskeletal pain, upper respiratory tract infection, bruising, rash, nausea, fever, neutropenia and constipation. These were reported in at least 20% of patients. Anaemia, neutropenia, pneumonia and thrombocytopenia were the most common serious adverse effects (grade 3 or 4) and occurred in 5% or more of patients.

In total, 26 patients died during the trials. Apart from progressive disease, causes included pneumonia (5 patients), sepsis (2 patients), secondary malignancy (2 patients), cardiac arrest (1 patient) and hypovolaemic shock (1 patient).

Bleeding-related adverse events were common with ibrutinib and ranged from bruising and nosebleeds to blood in the urine, gastrointestinal bleeding and intracranial haemorrhage. Warfarin, fish oil and vitamin E should not be given concomitantly with ibrutinib.

Atrial fibrillation is a risk with ibrutinib, particularly during acute infections or in people with a history of atrial fibrillation or other cardiac risk factors. Regular cardiac monitoring is recommended. Alternatives to ibrutinib should be considered in patients who need oral anticoagulants.

Blood counts should be monitored every month as severe neutropenia, thrombocytopenia and anaemia can occur. Skin cancers have been reported with ibrutinib so regular skin examination is important.

Ibrutinib caused a transient increase in lymphocyte count at the beginning of treatment in 75% of patients with chronic lymphocytic leukaemia and 35% of patients with mantle cell lymphoma. Lymphocytosis often occurred at the same time as a reduction in lymph node and spleen size and is thought to be a pharmacodynamic effect unrelated to progressive disease. Leukostasis (clumping of white blood cells) was occasionally reported and may be related to an increase in circulating lymphocytes. It can cause local hypoxaemia and bleeding which can present as headache, blurred vision, transient ischaemia, cerebrovascular accident and dyspnoea. Patients should be monitored closely and ibrutinib may need to be interrupted if this occurs.

Pharmacology and drug interactions

Ibrutinib is rapidly absorbed after oral administration and metabolised in the liver by cytochrome P450 (CYP) 3A4. The half-life is 4−6 hours and metabolites are eliminated in the faeces (90%) and urine (10%).

Co-administration of moderate or strong CYP3A4 inhibitors such as ketoconazole, clarithromycin, erythromycin or verapamil should be avoided. If they are needed, the ibrutinib dose should be reduced to 140 mg or interrupted for up to a week. Avoid grapefruit and Seville oranges as they can inhibit CYP3A4.

Strong CYP3A4 inducers and drugs that increase the pH of the stomach can decrease ibrutinib concentrations and are not recommended. St John's wort should also be avoided. As ibrutinib could theoretically inhibit intestinal P-glycoprotein, substrates of this transporter with a narrow therapeutic index (e.g. digoxin) should be taken at least six hours before or after the ibrutinib dose.

Conclusion

Ibrutinib offers another option for people with chronic lymphocytic leukaemia or mantle-cell lymphoma, particularly those who have relapsed after previous treatments. Adverse effects are common and sometimes severe so patient monitoring is very important with this drug.

References:


1. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013;369:32-42.
2. Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 2014;371:213-23.

3. Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med 2013;369:507-16.

Source: Australian Prescriber

## 243 charged in $712M Medicare-Medicaid fraud sweep

An eight-year, nationwide health care fraud crackdown resulted in 243 people being charged Thursday in connection with $712 million in alleged false Medicare and Medicaid claims, the Department of Justice announced. Forty-six licensed medical professionals were arrested in the health care fraud sweep, which is said to be the largest in the Justice Department's history. Miami remains a fraud hot spot, with 73 defendants charged with filing nearly $263 million in false Medicare claims. Arrests were also made in Brooklyn, N.Y., Los Angeles, Tampa, Fla., New Orleans, Detroit, Houston, Dallas and McAllen, Texas.

Source: The Washington Post

## U.S. appeals court again invalidates Teva MS drug patent

A U.S. appeals court on Thursday once again invalidated a patent held by Teva Pharmaceutical Industries Ltd on its top-selling multiple sclerosis drug Copaxone, clearing the way for the launch of a cheaper, generic version.

The decision is the second time the U.S. Court of Appeals for the Federal Circuit has reviewed the Teva patent and comes after the U.S. Supreme Court in January asked it to reconsider a previous decision to cancel the patent.

Source: Reuters

## Europe to develop database for identifying counterfeit medicines

The newly formed European Medicines Verification Organization has begun building a pharmaceutical repository system to help authorities identify fake drugs. Three software firms have signed agreements to begin database development, which is being established under the 2011 Falsified Medicines Directive.

Source: In-PharmaTechnologist.com

## Forthcoming Events:


## Annual General Meeting of IPA, Bengal Branch

**Date:** 05.07.2015

**Time: 5.00 pm**

**Venue:**

IPA Auditorium, 22 B Panchanontola Road, Kolkata-700029