Drug Information Bulletin

Drug Information Centre (DIC)
Indian Pharmaceutical Association
Bengal Branch
Tele fax: 033 24612776, E-mail: ipabengal.dic@gmail.com
Web Site: http://www.ipabengal.org
Contact: 09830136291

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Regulatory Affairs Division (RAD), IPA

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Editorial

Death due to Tuberculosis is a global problem and this problem has been aggravated by development of Multidrug Resistant TB (MDR-TB) and Extremely Drug Resistant TB (XDR-TB). In 2014 about 480000 people developed MDR-TB globally and about 9.7% of these cases were XDR-TB.

The Govt. of India started a Revised National Tuberculosis Control Programme in 1997 to eradicate TB. RNTCP followed the WHO recommendation of Directly Observed Short Course (DOTS) strategy and reaches over a billion people in 632 districts. One of the shortfalls of this programme is discontinuation of treatment because of several reasons. Now Govt. of India recognizes services of private facilities, and are also taking help of NGOs to facilitate the RNTCP Programme.

Indian Pharmaceutical Association (IPA) is working for TB Care and Control utilizing the services of the community pharmacists as they are more accessible to the TB patient. In 2011 World Health Organization (WHO) signed a MOU with FIP at Hyderabad during FIP congress in 2011. Thereafter TBC, Govt. of India has signed a MOU with IPA, PCI, SEARPharm Forum & AIOCD for care & control of tuberculosis. As per this agreement IPA has started working in different states involving Pharmacists working in community Pharmacy and have experienced extremely positive outcome.

In the recent past RNTCP has given direction to all state TB officers to involve community pharmacists in this programme. Along with all other states, State TB officer of West Bengal has given direction to the Chief Municipal Health Officer and CMOH of all districts for involving community Pharmacist in RNTCP for early detection, referral of TB suspects for treatment, DOT provision for TB treatment and generating awareness about TB and MDR-TB.

This is a golden opportunity for the community pharmacists to serve the community and hope they will extend all sorts of help for success of this programme.

Dr. Subhash C. Mandal
Editor
E mail: subhash.mandaldr@gmail.com

New Drug: Ceritinib for non-small cell lung cancer

Approved indication: non-small cell lung cancer

Zykadia

150 mg capsules

Australian Medicines Handbook section 14.2.4

Ceritinib is indicated for people with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer that has become resistant to crizotinib[1] or who cannot tolerate crizotinib. Rearrangements of the ALK gene lead to expression of oncogenic proteins which promote cell proliferation. As a tyrosine kinase inhibitor, ceritinib inhibits signalling of ALK. Up to 5% of people with non-small cell lung cancer have ALK-positive disease. These cancers are usually adenocarcinomas and are more common in non-smokers.

The approval of ceritinib is based on the results of a phase I (ASCEND-1)[2] and a phase II (ASCEND-2)[3] trial. Enrolled patients had advanced ALK-positive disease which had progressed despite other therapy. Many of them (60–71%) had brain metastases at baseline. Both trials were open-label without a control arm. Following treatment with ceritinib 750 mg once daily, 39–56% of patients had a partial or complete response, measured by regular CT and MRI scans of their tumours. Median progression-free survival was 5.7–6.9 months and median overall survival was 14.9–16.7 months.[2,3]

Diarrhoea, nausea and vomiting were very common in a safety cohort (n=525), occurring in 84%, 80% and 63% of patients respectively. Approximately 5% of these effects were serious. Grade 3 and 4 increases in liver enzymes were also very common and monitoring before and during treatment is important as dose reductions or interruptions may be required.

QT interval prolongation occurred in 6.5% of patients taking ceritinib. This was serious in some cases and the dose had to be reduced or discontinued. Ceritinib is not recommended in patients with congenital long QT syndrome or those taking drugs that prolong the QTc interval such as domperidone. Monitoring for electrolyte disorders is also important. Bradycardia was reported in 1.9% of patients and ceritinib should not be given with other drugs that have the same effect, such as beta blockers. Heart rate and blood pressure should be monitored regularly.

Severe and sometimes fatal pneumonitis has been reported with ceritinib and it was one of the most common reasons for permanent discontinuation in the trials, along with pneumonia. Other serious adverse effects included hyperglycaemia (5% of patients) and pancreatic toxicity (3%).

The recommended dose of ceritinib is 750 mg (5 capsules) taken at the same time each day. Capsules should be taken on an empty stomach (≥2 hours before or after a meal) as food increases exposure to the drug. Capsules should not be crushed or chewed.

Peak plasma concentrations are reached 4–6 hours after administration. The terminal half-life in plasma is 31–41 hours and steady state is reached after 15 days. Ceritinib is primarily metabolised by cytochrome P450 (CYP) 3A and most of the dose is excreted in the faeces. Moderate–severe hepatic impairment may increase plasma concentrations of ceritinib so the drug is not recommended in these patients.

Ceritinib is a substrate of CYP3A and P-glycoprotein. Strong CYP3A inhibitors (e.g. ketoconazole and ritonavir) can increase ceritinib concentrations, and inducers (e.g. carbamazepine, phenytoin, St John's wort) can decrease them. Concomitant use of these drugs should be avoided if possible and patients should be advised not to drink grapefruit juice. If a strong CYP3A inhibitor is needed, the ceritinib dose should be reduced by one-third. Caution is urged with inhibitors and inducers of P-glycoprotein.

Ceritinib may inhibit CYP3A and CYP2C9 directly so it can affect drugs that are metabolised by these enzymes. Doses of

interacting drugs may need to be reduced and drugs with a narrow therapeutic index such as fentanyl, phenytoin and warfarin should be avoided.

The solubility of ceritinib decreases as gastric pH increases therefore antacids, proton pump inhibitors and H_2 receptor antagonists can potentially reduce ceritinib's bioavailability and effect.

Up to half of the patients in the trials responded to ceritinib and on average their response lasted around 8–9 months. However, there were no comparators in the studies so it is not known how ceritinib compares to other options. Given the drug's toxicity, the benefits of treatment need to be balanced against the risk of serious and sometimes fatal adverse effects.

References

1. Crizotinib. Aust Prescr 2014;37:100-7.
2. Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, Camidge DR, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol 2016;17:452-63.
3. Crinò L, Ahn MJ, De Marinis F, Groen HJ, Wakelee H, Hida T, et al. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: Results from ASCEND-2. J Clin Oncol 2016;34:2866-73.

Canagliflozin Risk of lower limb amputation

The NPRA has updated the local package insert of canagliflozin (Invokana®) to include the risk of lower limb amputation. In addition, the product registration holder of canagliflozin has issued a DHPC letter on this safety issue in agreement with the NPRA. Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor that is used for the management of Type II Diabetes mellitus. Canagliflozin was registered in Malaysia in 2016. At the time of this publication, the NPRA had not received any ADR reports related to this product.

Reference: MADRAC Newsletter, NPRA, Volume 21, December 2016 (See page 12 potential risk of toe amputation with SGLT2 inhibitors in EU)

Fluoroquinolones Potential risk of persistent and disabling side effects

Health Canada has recommended updating the safety information for all fluoroquinolone products to include information about the risk of persistent and disabling side effects including tendonitis/tendinopathy, peripheral neuropathy and central nervous system disorders. Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin) are antibiotics which are authorized to treat many types of bacterial infections including urinary tract and respiratory infections. Health Canada started a safety review following a review done by the US FDA on systemic fluoroquinolone drugs. The Health Canada safety review focussed on serious known side effects that included: tendonitis/tendinopathy, peripheral neuropathy, worsening of myasthenia gravis, hypersensitivity and serious skin reactions, mental disorders, depression and suicide/self-injury, convulsions, cardiovascular disorders, phototoxicity and vision disorders. At the time of the review, Health Canada identified 115 reports of persistent and disabling side effects associated with the use of fluoroquinolones. In 78 of these reports, a probable (29 reports) or possible (49 reports) causal link could bemade between the use of fluoroquinolones and persistent disability. In the remaining cases, there was either not enough information available or it was unlikely that the reports of persistent disability were related to the use of fluoroquinolones. Most of the side effects that were reported in the 115 reports and linked to persistent disability included tendonitis/

tendinopathy, peripheral neuropathy and central nervous system disorders. The side effects of tendinopathy, peripheral neuropathy and central nervous system disorders are included in the current safety information. However, the possibility of persistent duration of these events was not included in the safety information for all fluoroquinolone products. There was little information in the scientific and medical literature on persistent and disabling nature of side effects reported with fluoroquinolone use. Health Canada's review concluded that some of the known side effects, specifically tendonitis/tendinopathy, peripheral neuropathy and central nervous system disorders, already linked to the use of fluoroquinolones, may be persistent and/or disabling.

Reference: Summary Safety Review, Health Canada, 23 January 2017 (www.hc-sc.gc.ca) (See WHO Pharmaceuticals Newsletters No.5, 2016: Disabling and potentially permanent adverse effects of the tendons, muscles, joints, nerves, and central nervous system in the US and No.3, 2016: Restricting use in the US)

DCGI/MISC/2017 (51)
Directorate General of Health Services
Central Drugs Standard Control Organisation
Office of DCG (I)

FDA Bhawan,
Kotla Road, New Delhi- 110002

16th May, 2017.

Dear Colleagues,

As all of you are aware, in terms of the existing provisions of the Drugs and Cosmetics Acts and thereunder Rules relating to new drug approval, as defined in Rule 122(E), prior approval of the Licensing Authority defined under Rule 21(b) is required before granting licence for manufacture for sale or distribution by the State Licensing Authority.

2. Instructions have been issued from time to time to ensure that in all cases regarding approval as new drugs including FDCs, the law/rules should be followed meticulously. Drug regulators of some of the manufacturing States have complained that the licensing authorities of certain States and UTs continue to grant licenses for manufacture of new drugs including FDCs without prior approval of the DCG (I).

3. Since, the practice as indicated above, if true, is illegal and not in conformity with the law and would have disastrous consequences, may I request you to ensure that this practice be stopped forthwith, if it has not already been discontinued. I would also strongly urge you to ensure that any such licences issued may also be cancelled and a report sent to me at the earliest possible.

Yours faithfully

(Dr G. N. Singh)
Drugs Controller General (India)

ALL DRUG CONTROLLERS OF STATES/UTs