



Drug Information Bulletin

Drug Information Centre (DIC)

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Editorial

The recent resolution adopted by the United Nations Human Rights Council (UNHRC) on 1st July is a land mark on access to medicines. This resolution was proposed by a host of developing countries like- Brazil, China, Egypt, India, Indonesia, Senegal, South Africa and Thailand which is related with intellectual property rights, trade agreements and access issues. The resolution – Access to medicines in the context of the right of everyone to the enjoyment of the highest attainable standard of physical and mental health was adopted by consensus though there was steep objection raised from some developed countries. The core issue was "on the primacy of human rights over international trade, investment and intellectual property regimes". The World Health Organization in its World Medicines Situations Report of 2011 states that at least one-third of the world population has no regular access to medicines. Experts opined that "The existing global framework does not allow the fruits of medical innovation to be equitably shared in particular to those most in need of them," This has resulted in skyrocketing prices for life-saving medicines and vaccines promoting discriminatory access to medicines. Every year 100 million are pushed into poverty and 150 million people suffer financial catastrophe because of out-of-pocket expenditure on health services globally. The resolution notes that "actual or potential conflicts exist" between the WTO's implementation of the TRIPS agreement and the realization of economic, social and cultural rights in relation to restrictions on access to patented pharmaceuticals and the implications for the enjoyment of the right to health. It urges member states to make full use of TRIPS flexibilities. India has utilized some of these flexibilities during framing its Patent Act 2005. Hope its efforts will continue to full utilization of the flexibilities and will protect the same.



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New Drug: Ramucirumab for gastric cancer

Approved indication: gastric cancer

Cyamza (Eli Lilly)

vials containing 100 mg in 10 mL and 500 mg in 50 mL as concentrate

Australian Medicines Handbook section 14.2.1

Ramucirumab is indicated for patients with advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma when the disease has progressed after cytotoxic chemotherapy. This drug is used in combination with paclitaxel or as monotherapy if paclitaxel cannot be given.

Ramucirumab is a monoclonal antibody that binds to the vascular endothelial growth factor (VEGF) receptor 2. This blocks the binding of several vascular endothelial growth factors (A, C and D) to the receptor. Signalling mediated by these growth factors in endothelial cells is important in the progression of gastric cancer.

The efficacy and safety of ramucirumab has been assessed in two trials – RAINBOW¹ and REGARD.² The trials enrolled patients who had locally advanced or metastatic gastric adenocarcinoma which had progressed after chemotherapy with platinum, fluoropyrimidine or both. Patients with a history of arterial thromboembolic events, gastrointestinal bleeding, or uncontrolled hypertension were excluded from the trials. Participants received treatment until their disease progressed (confirmed by radiography) or they had unacceptable adverse effects. In both trials, the primary end point was overall survival.

The RAINBOW trial randomised patients to ramucirumab plus paclitaxel or placebo plus paclitaxel. Ramucirumab (8 mg/kg) or placebo was given on day 1 and 15 and paclitaxel (80 mg/m²) was given on days 1, 8 and 15 of a 28-day cycle. Median overall survival was significantly longer in the ramucirumab arm than in the placebo arm (9.6 vs 7.4 months) (see Table).¹

In the REGARD trial, patients were randomised to ramucirumab monotherapy (8 mg/kg fortnightly) or placebo. All

participants received best supportive care. Although median overall survival times were generally shorter in this trial, ramucirumab significantly prolonged survival compared with placebo (5.2 months vs 3.8 months)²

In the RAINBOW trial, the most common adverse events with ramucirumab were fatigue (56.8%), neutropenia (54.4%), decreased appetite (40%), abdominal pain (36%), nausea (35.1%), leucopenia (33.9%), diarrhoea (32.4%), epistaxis (30.6%), vomiting (26.9%), peripheral oedema (25%), hypertension (23.8%), stomatitis (18%), proteinuria (16.5%) and thrombocytopenia (13.1%). All of these events were more common with ramucirumab than with placebo. There were six deaths that were thought to be related to ramucirumab plus paclitaxel. Causes included sepsis, septic shock, malabsorption, gastrointestinal haemorrhage and pulmonary embolism.¹

The most common adverse events with ramucirumab in the REGARD trial included fatigue (35.5%), abdominal pain (28.8%), decreased appetite (24.1%), vomiting (19.9%), hypertension (16.1%) and bleeding (12.7%). The five deaths thought to be related to ramucirumab were due to myocardial infarction, gastric haemorrhage, intestinal perforation (2 cases) and pneumonia.²

As hypertension can be a problem with ramucirumab, blood pressure should be monitored regularly. If it occurs, treatment should be interrupted until blood pressure is controlled.

Although patients with a history of thromboembolic events or gastrointestinal bleeding were excluded, myocardial infarction, cardiac arrest, cerebrovascular accident, cerebral ischaemia, gastrointestinal perforations and gastrointestinal bleeding have been reported with ramucirumab. These events have been fatal in some cases and treatment should be stopped if patients show symptoms. Blood clotting should be monitored in those with an increased risk of bleeding. Regular blood counts are also

important as neutropenia was common with combination ramucirumab therapy.

As ramucirumab can affect angiogenesis, the drug could potentially reduce wound healing. Treatment should be stopped four weeks before elective surgery and only started again after adequate healing.

Interactions with other drugs have not been observed with ramucirumab. The drug is diluted and given by intravenous infusion over 60 minutes. Infusion reactions can occur and are more common during the first and second infusion. Premedication to prevent infusion reactions is recommended. Antibodies to ramucirumab were detected in 2–3% of patients. However, these were found not to be neutralising antibodies.^{1,2}

Although ramucirumab improves the survival times of patients with advanced or metastatic gastric cancer, the benefit is modest. In the trials, median survival was prolonged by 8–9 weeks with ramucirumab and paclitaxel, and by 5–6 weeks with ramucirumab alone. Adverse reactions are common with ramucirumab and some are fatal so patient

References:

1. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224-35.
2. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014;383:31-9.

Ref. *Aust Prescr* 2016;39:63-4

Anticholinergic drugs possible cognitive problems in the elderly

The Saudi Food and Drug Authority (SFDA) has notified health-care professionals that certain anticholinergic drugs might be

associated with cognitive impairment and an increased risk of memory loss, known as dementia, in elderly patients. Anticholinergic drugs are widely used for treatment of various clinical conditions including vomiting, gastrointestinal spasms, bladder problems, Parkinson's disease, and depression. In 2015, the SFDA reviewed all available evidence on the association between anticholinergic drugs and cognitive impairment in older adults. The SFDA concluded that there is a potential risk of cognitive impairment and dementia with long-term use of anticholinergic drugs and the general awareness about this risk is low. The SFDA has advised healthcare professionals to consider the lowest effective dose of anticholinergic drugs with regular monitoring for signs of confusion or dementia in elderly patients particularly when prescribing any of these drugs for a long-term use.

Reference: Saudi Vigilance, Saudi Food and Drug Authority, 24 May 2016

Pertuzumab risk of Stevens-Johnson Syndrome: limited evidence

Health Canada has concluded that the evidence to support a link between the use of pertuzumab (Perjeta®) and the risk of Stevens - Johnson syndrome is limited. Pertuzumab is used in combination with other treatments to treat patients with breast cancer that has spread to other parts of the body. During routine review of information received from the manufacturer, Health Canada identified a possible risk of Stevens - Johnson syndrome which triggered Health Canada to conduct a safety review. At the time of the review there were no reports of StevensJohnson Syndrome linked to use of pertuzumab that originated from Canada. In addition, there were no reports identified in the literature. The reports received from the manufacturer were limited by missing information and presence of other contributing factors. The Canadian prescribing information already includes information regarding Stevens-Johnson Syndrome in one or two other

medications that are used in combination with pertuzumab. Health Canada has asked the manufacturer to continue monitoring for this risk worldwide.

Reference: Summary Safety Review, Health Canada, 4 April 2016 (www.hc-sc.gc.ca)

India may soon get treatment for Hepatitis C

A latest breakthrough treatment for the deadly [Hepatitis C](#) virus could soon be available in India as 11 Indian firms have been given licenses by its American manufacturer following an approval from US authorities.

The drug called [Epclusa](#) which is developed to treat all genotypes of the Hepatitis C virus by Gilead Sciences in its latest breakthrough treatment was last week approved by the [US Food and Drug Administration](#) (FDA).

The deadly Hepatitis C virus afflicts as many as 150 million people worldwide and possibly 12 million in India.

This pan-genotypic treatment does not require gene-type testing, eliminating the need for costly gene-type diagnostics, allowing doctors and specialists the ability to prescribe the medicine to anyone who tests positive for Hepatitis C, by taking one pill a day for 8-12 weeks before a cure is achieved.

"The approval of Epclusa represents an important step forward in the global effort to control and potentially eliminate [HCV](#) as it provides a safe, simple and effective cure for the majority of HCV-infected patients, regardless of genotype," said Ira Jacobson, MD, chairman of the Department of Medicine at Mount Sinai Beth Israel, New York and a principal investigator in the Epclusa clinical trials.

"Building on the established backbone of sofosbuvir, Epclusa demonstrated

consistently high cure rates across all genotypes, including among patients with genotype 2 and 3, who traditionally have required ribavirin or other multi-pill regimens," he said.

As part of its effort to make it an affordable treatment, Gilead Sciences, together with its 11 partners in India, are pioneering a Voluntary Licensing model that transfers technology and Intellectual Property for latest treatments and cures for viral Hepatitis and HIV. Gilead, in 2014, licensed its newly-approved HCV regimens to 11 of India's pharmaceutical companies, including the prospective Epclusa, which had not yet been cleared by the US FDA. "This forward thinking strategy opened for these Indian companies the market across all of India for generic versions of these drugs, plus the market for 100 other countries," an industry source said.

Because of India's capabilities in generic manufacturing, where quality and low cost co-exist hand in hand, Gilead Sciences recognised that to expand patient access and to deploy these life-saving cures to low income countries around the world to the patients who need treatment most.

It would be mutually beneficial to license the Intellectual Property for its new HCV medicines to companies in India which had already established supply chain linkages with countries across Africa, Asia, Eastern Europe, Mongolia, and other hard to penetrate markets, industry sources said.

Forthcoming Event

IPA Convention-2016

23rd July 2016

Venue: Pt. Ravishankar Shukla University auditorium, University Institute of Pharmacy, Raipur, Chhattisgarh.

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