Drug Information Bulletin

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Content

Editorial

WHO is publishing Model List of Essential Medicines since 1977 which is being updated every 2 years and the latest one is 19th edition published 1n the year of 2015. They also publishing Model List of Essential Medicines for the Children since 2002 and the latest one being the 5th version published in 2015. The list presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment. WHO is publishing Model Formulary of the medicines included in the Model List of Essential Medicines to provide independent information on essential medicines for pharmaceutical policy-makers and prescribers worldwide. For each medicine the Formulary provides information on use, dosage, adverse effects, contraindications and warnings, supplemented by guidance on selecting the right medicine for a range of conditions. WHO has adopted a specific structure and sections like Model List of Essential Medicines, but **any country or organization** can adopt any other structure for their own purpose. As a result like several countries round the globe Government of India has published 4th edition of National Formulary of India in 2011. Govt. of India has earlier published three versions in the year of 1960, 1966 and 1979. There are several other Formularies published by several organizations to meet their specific need which is not always common with other Like- Essential Drug Formulary 2006 published by Delhi Society for Promotion of Rational Use of Drug, Hospital Formulary of SRM University, India. Adoption of formularies at the National, Regional & Institutional level is useful for providing independent information on medicines used by the concerned health facilities.

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New Drugs: Everolimus

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may have been limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Certican (Novartis)

0.25 mg, 0.5 mg and 0.75 mg tablets

Approved indication: transplantation

Australian Medicines Handbook section 14.1

Everolimus is a derivative of the immunosuppressant drug sirolimus. It has been approved for use by patients receiving a heart or kidney transplant.

Although patients' survival after transplant has improved, problems may develop in the long term. For example, treatment with cyclosporin can damage the transplanted kidney and vasculopathy may complicate heart transplants. Everolimus may therefore have a role in preventing organ rejection because it inhibits cell proliferation. This inhibition includes vascular smooth muscle cells as well as T-cells.

Treatment begins as soon as possible after transplantation. Peak concentrations occur within two hours of an oral dose, but absorption is reduced by food. Steady state concentrations are reached within four days. Everolimus is metabolised by liver enzymes including cytochrome P450 3A4. Most of the metabolites are excreted in the faeces. The half-life of everolimus is approximately 28 hours.

Everolimus was compared with azathioprine in patients following heart transplantation. These 634 patients were also treated with cyclosporin, corticosteroids and a 'statin'. The end point of the study was a mixture of death or rejection. After 12 months, 52.8% of the azathioprine group had reached this end point. This was significantly more than the 41.6% of the 209 patients given everolimus 1.5 mg, and the 32.2% of the 211 patients given everolimus 3.0 mg.[1]

Studies in renal transplantation used mycofenolate mofetil as a comparator. Rejection had occurred by six months in 23.5% of the mycofenolate group, 21.6% of those taking everolimus 1.5 mg and 18.2% of those taking everolimus 3.0 mg.

Two studies used everolimus to lower the dose of cyclosporin used after renal transplantation. Although there was no comparator arm in the studies, both doses of everolimus were associated with satisfactory renal function after six months.[2]

As rejection occurs more frequently with lower concentrations, the blood concentration of everolimus must be monitored regularly. More frequent monitoring will be needed if the patient is started on a drug which inhibits (ketoconazole) or induces (rifampicin) CYP3A4.

Adverse events occur in almost everyone treated with everolimus. Approximately 10-22% of patients will discontinue treatment because of adverse events. These include anaemia, leucopenia, thrombocytopenia and infections.[1,2] In the heart transplant study significantly more bacterial infections occurred in the everolimus group. Even if the patients are taking 'statins' their triglyceride and cholesterol concentrations are likely to increase.[1]

Managing patients after transplantation requires balancing the risk of organ rejection against the adverse effects of immunosuppression. Further study will be needed to define the place of everolimus. The results of a Cochrane review of the effects of everolimus and sirolimus in renal transplantation are not yet available.[3]

References

1. RAD B253 Study Group. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med 2003;349:847-58.
2. Vitko S, Tedesco H, Eris J, Pascual J, Whelchel J, Magee JC, et al. Everolimus with optimized cyclosporine dosing in renal transplant recipients: 6-month safety and efficacy results of two randomized studies. Am J Transplantation 2004;4:626-35.
3. Webster AC, Higgins G, Chapman JR, Craig JC. Sirolimus and everolimus for kidney transplant recipients. (Protocol) The Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD004290. DOI: 10.1002/14651858.CD004290.

Reference: Australian Prescriber, Vol.28, Issue. 3

Indian Status: Everolimus tablets 2.5mg. 5mg and 10mg has been approved by CDSCO on 08.06.2016 with an indication of "Treatments of adults patients with progressive, well differentiated, non-functional neuroendrocrine tumors (NET) of gastrointestinal (GT) or lungs origin with unresectable, locally advanced or metastatic disease"

With Condition:

1. "Warning: To be sold by retail on the prescription of Oncologist only."

French Government denies hiding drug-related birth defects study

French health authorities are denying claims they concealed a study on a drug used to treat epilepsy that caused birth defects.

Le Canard Enchaine weekly said the health ministry suppressed a study revealing that the drug was prescribed to more than 10,000 pregnant women between 2007 and 2014 while the potential risks for unborn children were known.

The ministry responded Wednesday that the study was launched a year ago and that its initial findings will be presented according to plans on Aug. 24 to parents whose children have been affected by the anti-convulsion drug Depakine, sold in France by pharmaceutical company Sanofi.

A study published in February estimated that there had been around 450 cases in France of children exposed to the drug during pregnancy who had congenital defects.

Source: The Associated Press

US medical device maker Alere sets up Rs 150-crore manufacturing facility in India

US-based portable molecular diagnostic products firm Alere Inc has set up its first integrated manufacturing facility in Manesar, near Delhi.

The unit will produce over 150 million cartridges that can be used for rapid tests for infectious diseases including malaria, dengue and HIV. The Rs 150-crore facility, spread across 180,000 sq. ft, will generate 300 new jobs and is capable of doubling its capacity, the company informed.

"Alere believes in Prime Minister Narendra Modi's vision of 'Make in India', and is committed to improving access to affordable rapid diagnostics in India and throughout the Asia-Pacific region through this new world-class manufacturing facility. The new factory will produce rapid tests for infectious diseases including Malaria, Dengue and HIV, and export them across Asia Pacific, a region heavily impacted by these diseases," Namal Nawana, CEO & President, Alere Inc., said.

Alere employs 600 people in India and is the market leader in point-of-care diagnostic tests for dengue and malaria. The company is working closely with state governments and institutions like National Aids Control Organisation and Clinton Foundation.

The company will continue to focus on cardio metabolic diseases, infectious diseases and toxicology (Drugs of Abuse) solutions in India by providing affordable, sensitive, specific, user-friendly, devices for disease control & management, stated a press release.

The new facility is part of the company's Asia-Pacific expansion plan, as it wants the Indian facility to cater to the growing demand for rapid diagnostics in APAC Region.

Source: Business Today

China proposes revised Drug Registration Rules

CFDA has issued new proposals to revamp China's Drug Registration Rules (DRR) that offer a mixed bag of updated policies that could stymie or promote innovation, according to life sciences legal specialists in China.

The revisions, which are tantamount to revising the Food, Drug and Cosmetic Act in the U.S., are based on State Council reforms released last year that offered the prospect of eliminating a backlog of drug reviews, updating China's drug classification system and reforming clinical trial rules to allow parallel drug development in and outside of China (see BioCentury Extra, Aug. 19, 2015).

According to law firm Ropes and Gray, the revised rules would alter innovator exclusivity by eliminating the linkage between patent protection and drug approvals, allowing CFDA to approve products that infringe on active patents. Sponsors of competing applications would be required to provide a statement to CFDA stating that the product does not infringe.

The revision also would allow CFDA to review clinical trial authorization applications for products identical to innovator compounds during an innovator drug's post-approval monitoring period. Under the current rules, CFDA is not allowed to accept applications during the monitoring period. The agency reviews applications within two years of any relevant patents' expiration, and cannot approve follow-on products before the patents expire.

Tony Chen, a partner at law firm Jones Day who specializes in IP, told BioCentury the changes would represent a weakening of IP protection in the country, adding that statements on infringement provided by competing applicants would not be reviewed critically by CFDA. He warned the change could cause China to fall behind other countries -- notably Korea, which has stronger IP protection -- in innovative development.

On clinical trials, the proposed revision would allow companies to include China in international trials during Phase I development, rather than Phase II, by doing away with the distinction between international multi-center clinical studies and drug registration studies. The studies must be conducted explicitly for the purpose of regulatory approval.

The modified rules also would eliminate statutory timelines for CFDA to review applications and prohibit sponsors from marketing APIs without an approved

drug product marketing application. Ropes Partner Katherine Wang said the revision would effectively force API manufacturers to seek marketing approval of drugs, and in the longer term would likely reduce the number of API manufacturers.

The revisions also would obligate application sponsors to review the performance of any third-party service providers and appoint dedicated regulatory specialists to handle communications with CFDA.

Wang said it is too early to predict the revisions' potential effects. She noted that China's government "in principle supports indigenous innovation," and said multinationals should re-evaluate their strategies in China if the changes are enacted.

CFDA is accepting comments on the new policy until Aug. 26.

Pfizer adds to list of drugmakers under lens for deviating from good manufacturing practices

Pfizer is the latest addition to an expanding list of drug makers found deviating from good manufacturing practices in India. In the last week of June, a high profile team drawn from world's four leading regulators identified a number of deficiencies at the company's Irungattukottai facility, near Chennai. Pfizer has temporarily stopped production at the site.

The site, which makes generic injectable drugs, is grappling with adverse reviews for a few years. It was served a warning letter by the US Food and Drug Administration (FDA) in 2013, which was followed up with a handful of observations.

Pfizer confirmed to ET about the inspection. It was led by UK's Medicines and Healthcare products Regulatory Agency (MHRA) and included US FDA, Therapeutic Goods Administration of Australia and Health Canada, the Canadian drug regulatory agency .

The New York-headquartered pharmaceutical giant informed "it temporarily paused production at the site to allow an assessment of observations by appropriate experts". It added, "Our colleagues are fully engaged and working towards resuming production as soon as possible. The temporary pause in manufacturing is being utilized to review the observations, to develop a holistic improvement plan and also to provide additional training to our colleagues at the site".

The injectables unit was formerly owned by Hospira, the injectables maker that Pfizer acquired last year as part of a global $17 billion deal. Hospira had acquired it in 2009 from Orchid Chemicals in a broader $400 million transaction.

"A holistic plan is being developed to address specific inspection observations and to implement enhancements to site operations," Pfizer said, stating the site is dedicated for exports and does not manufacture for the domestic market.The company ruled out any impact on its employees at the site as a result of the latest inspections.

The USFDA and MHRA submitted their inspection observation reports, which Pfizer said it has reviewed in depth. "The site has formally responded to both these agencies and is working diligently to address the specific inspection findings and implement enhancements to site operations," it noted.

In a statement to ET a spokesperson for Health Canada said a number of deficiencies were identified during the same inspection. "The company is responsible for implementing corrective and preventative actions to address the deficiencies. The information resulting from this inspection is currently under review by the joint inspection team," the regulatory body added.

An official spokesperson for the US FDA said it does not publicly disclose information about potential or ongoing inspections. Questions to MHRA were not answered until press time.

Forthcoming Events: