

- or not to use? *Med J Aust.* 2003 Jun 16;178(12):630-3.
9. McClung MR. The menopause and HRT. Prevention and management of osteoporosis. *Best Pract Res Clin Endocrinol Metab.* 2003 Mar; 17(1):53-71.
 10. Cauley JA, Black DM, Barrett-Connor E, et al. Effects of hormone replacement therapy on clinical fractures and height loss: The Heart and Estrogen/Progestin Replacement Study (HERS). *Am J Med.* 2001;110:442-450.
 11. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605-613.
 12. Torgerson DJ, Bell-Syer SEM. Hormone replacement therapy and prevention of nonvertebral fractures. *JAMA.* 2001;285:2891-2897.
 13. Farrell E. Medical choices available for management of menopause. *Best Pract Res Clin Endocrinol Metab.* 2003 Mar;17(1):1-16.
 14. Mary Beth O, Connell, Pharm D. Prevention and Treatment of Osteoporosis in the Elderly. *Pharmacotherapy* 1999;19:84-100.
 15. T John Martin, Vivian Grill. Bisphosphonates - Mechanisms of action. *Australian Prescriber.* 2000;23:130-132.
 16. Karpf DB, Shapiro DR, Seeman E, Ensrud KE, Thompson D, Harris ST, et al. Prevention of nonvertebral fractures by alendronate: a meta-analysis. *JAMA* 1997;277:1159-64.
 17. Harris ST, Watts NB, Genant HK, Keller M, Miller PD, Brown J, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: an randomized controlled trial. *JAMA* 1999;282:1344-52.
 18. Balfour JA, Goa KL. Raloxifene. *Drugs Aging* 1998;12:335-341.

19. Overgard K, Hansen MA, Jensen SB, Christiansen C. Effect of calcitonin given intranasally on bone mass and fracture rates in established osteoporosis: a dose-response study. *BMJ* 1992;305:556-61.
20. Braga PC. Calcitonin and its nociceptive activity: animal and human investigations 1975-1992. *Agents Actions* 1994;41:121-31.
21. Knight DC, Eden JA. A review of the clinical effects of phytoestrogens. *Obstet Gynecol.* 1996;87:897-901.
22. Kansra U. Osteoporosis - Medical Management. *JACM* 2002;3(2):128-40.
23. Pak CYC and Rubin CD. Sustained release sodium fluoride in the management of established postmenopausal osteoporosis. *Am J Med Sci.* 1997;313:23-32.
24. Marcus R. Agents affecting calcification and bone turnover. In: Hardman JG, Limbird LE, Molinoff PB, Gilman RW, Gilman AG ed.- *Goodman and Gilman's: The Pharmacological Basis of therapeutics* 9th ed. New York: McGraw Hill Inc. 1996:1519-46.
25. Reginster JY. Miscellaneous and experimental agents. *Am J Med Sci.* 1997;313:33-40.
26. Wasnich RD, Davis JW, He YF, Petrovich H, Ross PD. A randomised, double-masked placebo-controlled trial of chlorthalidone and bone loss in elderly women. *Osteoporos Int* 1995;5:247-51.
27. Patel S. Current and potential future drug treatment for osteoporosis. *Ann Rheum Dis.* 1996;55:700-14.
28. Cardinali PC, Ladizesky MG, Veronica B, Cutrera RA, Mautalen C. Melatonin effects on bone: experiments facts and clinical perspectives. *J Pineal Rs.* 2003;34:81-87.

ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

The need for uniform ethical guidelines for research on human subjects is universally recognised. It has acquired a new sense of urgency as the critical issues in the area of biogenetic research involving human subjects have become acute. Apart from the mandatory *clinical trails* on new drugs, a number of *diagnostic procedures, therapeutic interventions and prevention measures* including the use of vaccines, are being introduced which involve human subjects. Further the advent of *new medical devices and radio-active materials* and therapeutic benefits of *recombinant DNA products* have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

Any research using the human beings as subjects shall bear in

mind the following principles of : i) **essentiality**, (ii) **voluntariness**, **informed consent**, (iii) **non exploitation**, (iv) **privacy and confidentiality**, (v) **precaution and risk minimisation**, (vi) **professional competence**, (vii) **accountability & transparency**, (viii) **maximisation of public interest and distributive justice** (ix) **institutional arrangements** (x) **public domain** (xi) **totality of responsibility** and (xii) **compliance**.

Recent advances in the field of **Assisted Reproductive technologies, organ transplantation, Human genome analysis, and gene therapy** promise unquestionable benefits to mankind. At the same time, they raise many questions of law and ethics, stimulating public interest and concern.

(Source : ICMR Publication 2000)

Drug Profile

SIROLIMUS

Sirolimus is a carbocyclic lactone-lactam macrolide-antibiotic prepared through natural fermentation from the soil actinomycete *streptomyces hygroscopicus*. sirolimus first demonstrated antifungal activity but, due to its structural similarity to tacrolimus, it was used for its immunosuppressive activity.

Mechanism of action : Sirolimus inhibits T. Lymphocyte activation and proliferation that occurs in response to antigenic and cytokine stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, it binds to the immunophilin, FK binding protein-12 (FKBP-12), to generate an immuno-suppressive complex. The sirolimus; FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mammalian target of Rapamycin (MTOR) a key regulatory kinase. This inhibition suppresses cytokine-driven T cell proliferation, inhibiting the progression from the G1 to the S-phase of the cell cycle.

Pharmacokinetics : It is readily but poorly absorbed after oral administration with an estimated bioavailability of 15%. Once absorbed into systemic circulation, it easily enters cells because of its high lipophilicity. 95% of drug is bound to RBG, 3% is found in plasma and 1% in lymphocytes and granulocytes. It is 100 times more potent than cyclosporine probably because of increased binding to RBG and decreased binding to lymphocytes.

Metabolism & excretion : It undergoes extensive metabolism by the CYP 3A4 system both in liver and small intestine. It is also a substrate of the efflux pump, P-glycoprotein, which is also found in the intestinal wall. The terminal half life (t_{1/2}) of drug is long ranging from 57 to 62 hours suggesting that once - daily dosing is adequate. Over 90% of the drug is removed through the faeces, and only a minor amount (2.2%) is excreted in urine. No dosage adjustment is necessary in patients with renal dysfunction. It is not removed by dialysis. It is extensively metabolized in the liver; therefore dosage modification is necessary in patients with hepatic dysfunction; 1/3rd of the

recommended dose should be given to patients with mild to moderate hepatic dysfunction. Sirolimus is metabolized by the CYP3A4 enzyme system. Any agent that alters the concentration of cyclosporine is expected to alter sirolimus concentrations. these include both enzyme inducers (eg rifampin, phenytoin) and inhibitors (azoles-antifungal, erythromycin, diltzem)

Indication : It is Indicated for the prophylaxis of organ transplant rejection. It is recommended that sirolimus should be used initially in a regimen with cyclosporine and corticosteroids.

Dosage & Administration: It is to be given orally once a day. The initial dose of sirolimus should be administered as soon as possible after transplantation. A daily maintenance dose of 2 mg is recommended for use in renal transplant patients with a loading dose of 6mg. It should be taken consistently with or without food. It must be taken 4 hours before/after cyclosporine dose.

Adverse Effects : The commonly reported adverse effects include abdominal pain, asthma, back pain, chest pain, fever, headache CVS hypertension; *digestive* Constipation, Diarrhoea, dyspepsia, nausea, vomiting; *metabolic and nutritional* : increased creatinine, oedema, hypercholesterolemia, hyperkalemia hyperlipidemia, hypokalemia, Wt gain, peripheral oedema; *musculo skeletal* - arthralgias; *nervous system* - tremor, insomnia; *respiratory system* - dyspnoea, pharyngitis, URI; *hematological* - Anaemia, leukopenia, thrombocytopenia

Drug Interaction: Drugs that may increase sirolimus blood concentration include: *calcium channel blockers* - nifedipine, verapamil; *antifungal* - clotrimazole, fluconazole, itraconazole; *macrolide antibiotic* - clarithromycin, erythromycin; *prokinetic agents* - cisapride metoclopramide;

Drugs that may decrease sirolimus concentration include *anticonvulsants* carbamazepine, phenobarbitiv, phenytoin; *antibiotics* - rifabutin, rifapentine; *vaccinations* - vaccination may be effective during Sirolimus therapy.

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