



CAPRISA

CENTRE FOR THE AIDS PROGRAMME
OF RESEARCH IN SOUTH AFRICA



GENERIC APPROVAL

The FDA's "tentative" approval of a generic ARV from Aspen Pharmaceuticals in South Africa raises several questions. See Page 2

CAUTIONARY NOTE



New ARV data will mean a change in treatment regimens in TB patients. See Page 2



GILEAD Sciences' Director for International Operations - Africa, Robert Webster visited CAPRISA, 14 - 15 February 2005. See Page 3

New NIH policy on public access to research data

A far-reaching initiative that promises to streamline the release of research publications has been launched by the NIH.

As part of the broadening process they have urged scientists to speed up the public release of research publications with the aim of making up-to-the-minute relevant data available as an online public archive service.

The policy - the first of its kind for NIH - focuses on the free electronic access of research supported by the NIH, within 12 months of publication. The web-based archive will be managed by the National Library of Medicine (NLM), a component of NIH.

NIH's director Elias A. Zerhouni said that this exciting new venture would ensure the permanent preservation of vital published research. Scientists have the right, she said, to see the results of their work disseminated as quickly and broadly as possible and NIH was committed to helping scientists exercise this right.

Zerhouni said that in developing this policy, a concerted effort was made to balance the importance of this archive to NIH's public health mission, with the need to provide flexibility for authors, their institutions and publishers where immediate release is not possible.

The venture will get going on May 2 this year with several important goals in mind. These include:-

- creating a stable archive of peer-reviewed research publications from NIH-funded studies to ensure permanent preservation of vital research findings

- securing a searchable compendium of these publications that NIH and its awardees can use and manage more efficiently. This will create a better understanding of research portfolios, the monitoring of scientific productivity and ultimately help set research priorities
- making published results of NIH-funded research more readily accessible to the public, health care providers, educators and scientists.

The release of this policy follows months of intensive deliberations with representatives of patients and scientific organisations, researchers and publishers. NIH posted the draft policy for public comment last September and received and reviewed over 6000 public comments.

As part of the on-going efforts to implement this new policy, the NIH plans to establish a Public Access Advisory Working Group which will provide advice on implementation issues and assess progress in meeting the stated goals.

Authors have been strongly encouraged to exercise their right to specify that their articles will be made publicly available through the NLM's digital repository PubMedCentral (PMC) as soon as possible. More information about this searchable electronic archive can be found at <http://www.pubmedcentral.nih.gov>.

USEFUL WEBSITE

Additional information, including questions and answers and details regarding the Policy is available on the website: <http://www.nih.gov/>



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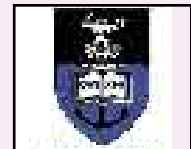
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FDA's "tentative" approval of generic ARVs raises key issues

On 25 January 2005, the US Food and Drug Administration (FDA) announced that it had given "tentative" approval of a co-packaged antiretroviral drug regimen manufactured by Aspen Pharmacare of South Africa for the treatment of HIV-1 infection in adults.

The product is a co-packaged presentation of lamivudine (3TC)/zidovudine (ZDV, or AZT) fixed dose combination tablets and nevirapine (NVP) tablets. This was immediately welcomed by many in the HIV/AIDS field, who saw the possibility of accessing quality-approved but lower cost ARVs.

Some might have been put off by the word "tentative" – was this product approved or not?

The FDA press statement explained that existing patents prevent Aspen from selling these products in the US, but that they had met "FDA's quality, safety and efficacy standards for US marketing".

GlaxoSmithKline holds valid patents on the 3TC/ZDV combination (sold as Combivir®) and Boehringer-Ingelheim holds patents on the NVP (sold as Viramune®).

If the new 3-drug combination cannot be sold in the US, why is the FDA giving it "tentative approval"? This has nothing to do with treating patients in the US, but is necessary to allow procurement of a lower-cost, generic ARV by programmes funded by President Bush's Emergency Plan for AIDS Relief (PEPFAR). PEPFAR currently funds treatment programmes in Botswana, Cote d'Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda and Zambia.

However, Aspen is also constrained by the conditions of its voluntary licenses from the two innovator firms, which restrict it to selling generic versions of their products to sub-Saharan Africa only.

Does this have any implications for CAPRISA, as a recipient of PEPFAR funding? The combination approved by the FDA is not the same as the regimens being used in the CAT programme, which follows the State rollout first-line choice of stavudine (d4T), lamivudine (3TC) and either efavirenz (EFV) or nevirapine (NVP).

In order to procure these and still comply with the PEPFAR requirement that the products bought be FDA approved, the CAT programme must still stick with branded, innovator products. In time, a more appropriate co-blistered presentation or fixed dose combination may become available. If it is to contain EFV, then the company making it will also need a voluntary license from the innovator, in this case MSD. A case of watch this space!



ANDY GRAY ASKS

What are the implications for CAPRISA's CAT programme as a recipient of PEPFAR funding?

CAPRISA visit by Gilead Sciences' Director for Africa



GILEAD Sciences' Director for International Operations - Africa, Robert Webster visited CAPRISA, 14 – 15 February 2005.

Mr. Webster is on a nine-country visit to Africa and spent two days touring the CAPRISA facilities in Durban and Vulindlela. He commented on the very high standard of the operation and the importance of the clinical work being conducted here.

His only regret was only having two days in Durban and he plans to return for a longer visit in June this year.

Gilead Sciences manufactures Viread® [tenofovir disoproxil fumarate] the first nucleotide analogue reverse transcriptase inhibitor approved by the FDA for the treatment of HIV infection

ARV drug safety alert prompts a rapid change in treatment practice

One of the challenges of working in the HIV/AIDS field is that knowledge changes so rapidly.

Practice must sometimes be based on inadequate data, so that when new data becomes available, rapid changes in practice may be necessary.

An example of this was provided on February 7, 2005, when the FDA and Roche Pharmaceuticals released a statement on the concomitant use of ritonavir-boosted saquinavir with rifampicin.

The manufacturers had informed the FDA of problems experienced in a phase I, randomized, open-label, multiple-dose clinical pharmacology study in healthy volunteers.

Of 28 patients given rifampicin 600 mg once daily together with ritonavir 100 mg and saquinavir 1000 mg twice daily, 11 (39.3%) had developed significant hepatocellular toxicity during the 28 day study period.

Transaminase elevations of up to >20 times the upper limit of normal values were noted. One subject was hospitalised. In all cases, the study medication was stopped. In all cases liver function tests returned to normal and clinical symptoms abated. No deaths occurred.

The problem here is that the package insert for both presentations of saquinavir (hard and soft gel capsules) lists concomitant rifampicin as a contraindication, as there is a known pharmacokinetic interaction. Rifampicin induces liver enzymes responsible for the metabolism of saquinavir, reducing the circulating concentration and therefore potentially leading to loss of efficacy and perhaps even the development of resistance.

Ritonavir, on the other hand, inhibits liver enzymes, boosting the levels of co-administered protease inhibitors such as saquinavir. Guidelines from various authorities had suggested that, if a protease inhibitor was needed in a patient receiving rifampicin, ritonavir-boosted saquinavir was the preferred option.

In the face of the new evidence of a safety problem, this option is no longer tenable. The START protocol will therefore have to be amended. The question is to what?

Two options seem possible – to either stop ARVs altogether until the patient has stopped taking rifampicin (at the end of TB treatment) or to find an alternative ARV regimen. Ritonavir-boosted Saquinavir would be used in patients unable to take efavirenz.

Nevirapine cannot be used with rifampicin either. The only options appear to be triple-nucleoside regimens, but these are themselves increasingly controversial. A lively debate is assured!

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A multi-institutional collaboration, incorporated as an independent non-profit AIDS Research Organisation

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<http://www.caprisa.org>

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Research update: January 2005

Study	Stage / site	Screened		No. Enrolled	
		Total (for month)	Cumulative (since study initiation)	Total (for month)	Cumulative (since study initiation)
Acute Infection	Phase I	50	390	9	67
	Phase II	1	3	1	3
CAT	Vulindlela	52	403	19	62
	CDC	40	187	17	56
Sero incidence	Vulindlela	58	712	23	264

Scientific Review Committee update: January 2005

Abstracts submitted for review		Manuscripts submitted for review		Ancillary studies submitted for review	
Total (for month)	Cumulative (since committee initiation)	Total (for month)	Cumulative (since committee initiation)	Total (for month)	Cumulative (since committee initiation)
1	36	0	6	0	1

NEW APPOINTMENT

Ms Anuska Naidoo, pharmacist at CDC, appointed from 1 February 2005.

CONTACT

Doris Duke Medical Research Institute
Nelson Mandela School of Medicine
University of KwaZulu-Natal
Private Bag X7
CONGELLA
4013
South Africa

Tel:
+27-31-2604555

Fax:
+27-31-2604566

E-mail: caprisa@ukzn.ac.za
Website: www.caprisa.org

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