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WHO issues guidance for doctors, governments, patients on what to do about delisted ARVs

Introduction

The World Health Organization this week issued a guidance note for doctors, patients, national regulatory authorities and national AIDS programmes on what to do following recent `delisting` of a number of WHO-prequalified antiretrovirals.

WHO recommends that in situations where prequalified substitutes are not available, patients should continue to take the delisted products rather than interrupt treatment, implying that so far, WHO has no evidence to suggest that the drugs are failing.

However, Daniela Bagozzi of the World Health Organization told HIV & AIDS Treatment in Practice: We don't want patients to take them unless there's absolutely no alternative. At the moment we don't know whether they are bioequivalent or not.

The guidance note comes nearly one month after WHO announced that it had delisted three products manufactured by Ranbaxy from its list of `prequalified` antiretrovirals due to irregularities in the research procedure and three months after two Cipla antiretrovirals were delisted.

The products are:

- Lamivudine 150mg plus stavudine 30mg and nevirapine 200mg tablet (Ranbaxy Laboratories Ltd, Dewas, India, Al strip of 10 or 60 in box, brand name Viro LNS)
- Lamivudine 150mg plus stavudine 40mg and nevirapine 200mg tablet (Ranbaxy Laboratories Ltd, Dewas, India, Al strip of 10 or 60 in box, brand name Viro LNS)
- Lamivudine 150mg plus zidovudine 300mg tablet (Ranbaxy Laboratories Ltd, Dewas, India, Blister pack of 60 or 100, brand name Virocomb)
- Lamivudine 150mg tablet (Cipla Ltd, Kurkumbh, India, blister pack of 10, brand name Duovir)
- Lamivudine 150mg plus zidovudine 300mg tablet (Cipla Ltd, Vikhroli, India, blister pack of 10, brand name Lamivir).

[Click here](#) to read a full report on the delisting of the Ranbaxy products.

[Click here](#) to read a full report on the delisting of the Cipla products.

[Click here](#) for WHO Guidance note: full text.

More information on the problems with the products

Specifically, WHO found serious discrepancies between the original results compiled by the CROs and the results presented to WHO by the manufacturers.

We have no idea where in the chain of events the data changed, Daniela Bagozzi told HIV & AIDS Treatment in Practice.

Cipla is now carrying out new studies and expects to submit all the new data on its delisted products by mid-September. Ranbaxy's managing director Brian Tempest says that new bioequivalence

studies for its delisted products may take most of the remainder of 2004 to complete.

WHO stresses that it has no specific evidence of a lack of bioequivalence, but given the discrepancies in the data, it has asked the companies to carry out new studies in research laboratories that follow all the international rules on good clinical research practice. The products do meet other quality specifications, including active ingredient purity, stability and manufacture in compliance with Good Manufacturing Practice, WHO stated this week.

The WHO decision has been confusing for many people because it is based on what appear to be procedural irregularities rather than hard evidence that the products in question fail to contain the right amounts of the active ingredient, or fail to produce blood levels in humans that are similar to the branded, originator products. This latter test is known as bioequivalence.

In a quandary

The delisting announcements have left many people confused about what to do. The International HIV/AIDS Alliance has been the principal recipient managing a Global Fund grant for antiretroviral therapy in Ukraine, and was caught out by the WHO decision. The Global Fund mandates that its money may only be used to buy WHO-approved generic products.

Susie McLean of the International HIV/AIDS Alliance told HIV/AIDS Treatment in Practice: The Alliance had placed an order for supplies of Cipla AZT/3TC tablet for 3000 people to be treated in the Ukraine, but just as we were about to start the treatment programme, the product was delisted. It was intensely frustrating after all the other delays in getting the programme up and running. It probably delayed the start of treatment by about one month. We had to buy replacement drugs from Glaxo SmithKline at a higher price.

In South Africa the Medicines Control Council has instructed that all stocks of Duovir should be recalled and that doctors should switch patients to equivalent products manufactured by Glaxo SmithKline or Thembalami.

[Click here to read a full report on that announcement.](#)

However, regulatory agencies in other countries where these products are available have not issued guidance.

But in other countries the lack of guidance reflects confusion about what to do, together with a lack of capacity to respond to the problem.

WHO's recommendations

WHO advised this week that decision-makers need to balance two considerations:

- These products may or may not be bioequivalent;
- Interruption of ARV treatment constitutes a serious risk for the individual and may have negative implications from a public health perspective.

In countries where bioequivalence is required, the national drug regulatory authority should consider one or more of the following actions:

- Request a confidential copy of the inspection report(s) from WHO;
- Temporarily waive its requirement of bioequivalence for these products as an emergency measure, requesting that the manufacturers submit data on new bioequivalence studies within

four months (if these deadlines are not met, consider withdrawing marketing authorisation);

- Do not release the products in stock for use until further evidence from new bioequivalence studies becomes available;
- Withdraw marketing authorisation for the products;
- Provide detailed information and advice to programme managers, prescribers and patients on the best ways to manage the situation without compromising the goals of treatment programmes.

Practical implications for programme managers

In countries where bioequivalence data are not required by the national drug regulatory authority there is no legal need to withdraw the products; and even in countries where these data are required, the authorities may (temporarily) decide not to withdraw them (see above). In all cases, a careful balance must be sought between the risks associated with the lack of proof of bioequivalence in these products and the individual and public health risk of interrupting treatment should no alternative medicines be found.

In general, switching to similar antiretrovirals (ARVs) from alternative, prequalified suppliers would be the most appropriate response, if and when such products are available. (see Annex 1 below) However, switching to non-prequalified ARVs is not advised since not only has their bioequivalence not been confirmed, but, in addition, other quality aspects have not been verified by WHO.

Recommended action:

- Consult with the national drug regulatory authority to establish the best course of action.
- Prepare and implement a communication strategy addressed to prescribers and patients.
- Take the necessary measures to switch to alternative prequalified products (listed in Alternative Products below).

In the second case, the following actions are recommended in specific situations:

- The procurement of de-listed drugs is considered, but they have not yet been ordered: De-listed products should not be ordered. Instead, other prequalified products should be ordered unless the de-listed medicines are reinstated on WHO's list of prequalified products.
- De-listed drugs have been ordered to continue or scale up treatment programmes: De-listed drugs that have been ordered, but not received, should not be accepted. In this case, alternative prequalified products should be ordered instead. However, if alternative suppliers are not immediately available and the non-acceptance of the ordered products could lead to an inability to continue or to start treating patients, the risk of withholding treatment is higher than that of providing medicines whose bioequivalence is not proven but which have, otherwise, been prequalified. In this case it would be justified to accept and use the de-listed products. For follow-up orders, only prequalified products should be used.

Practical implications for prescribers and patients

In principle, patients should discontinue using de-listed medicines and switch to other prequalified products. However, in many cases it will be difficult to find alternative prequalified products immediately. In this situation it is recommended that patients continue to use de-listed products, as the risk of interrupting treatment is higher than that of taking medicines whose bioequivalence is not proven but which have otherwise been prequalified. A switch to non-prequalified products is not recommended as their quality has not been documented by WHO.

The patient should be informed that there is no reason to believe

Continued use of the de-listed products is dangerous, and that

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suspending the treatment or switching to alternative ARVs whose quality has not been assured is far riskier.

Next steps by the manufacturers

The manufacturers have indicated that they will resubmit the products in question to a different laboratory for new bioequivalence studies. If and when those products and the laboratory meet the specified requirements, WHO will reinstate them in its list of prequalified medicines.

Next steps by WHO

- WHO will make available to national drug regulatory authorities, upon request and under confidential cover, the inspection reports on the de-listed products.
- As soon as new bioequivalence data of the de-listed products have been received WHO will arrange for immediate data assessment and site inspections, to minimise administrative delays in the potential re-listing of the products.
- WHO will send a letter to all manufacturers of prequalified products, asking them to take all necessary measures to ensure that the data submitted to WHO are correct and complete, and to check that CROs have followed the appropriate standards.
- As a matter of urgency, WHO will inspect all other CROs which have conducted bioequivalence studies for prequalified products, starting with priority medicines.
- For new applications, WHO will introduce inspections of CROs and laboratories for compliance with Good Clinical Practice and Good Laboratory Practice as a prerequisite for prequalification.
- WHO will also start a programme of inspections of manufacturers of Active Pharmaceutical Ingredients (raw materials), with an initial focus on antiretrovirals.

Alternative prequalified products and suppliers

- Lamivudine 150 mg plus zidovudine 300 mg tablet (GSK), blister (60), bottle (60)
- Lamivudine 150 mg plus zidovudine 300 mg tablet (Hetero), blister (10), bottle (60)
- Lamivudine 150mg plus stavudine 40 mg and nevirapine 200 mg tablet (CIPLA), bottle (60)
- Lamivudine 150mg plus stavudine 30 mg and nevirapine 200 mg tablet (CIPLA), bottle (60)
- Lamivudine 150 mg tablet (GSK), 10 mg/ml oral solution (GSK), bottle (60) and bottle (240 ml), respectively
- Lamivudine 150 mg tablet (Hetero), blister (10), bottle (60)
- Lamivudine 150 mg tablet (Strides), blister (10), bottle (60)

about HATiP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

For further information please visit the HATIP section of aidsmap.com