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Quality-Control Analysis of Generic Nevirapine Formulations in the Developing World: An Initial Report

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ABSTRACT

Background: Generic antiretroviral (ARV) medications have recently become available in many developing countries at costs that are far cheaper than discounted proprietary agents. There are currently no publicly available data describing the integrity (drug content vs. label claim) of these preparations. We analyzed the content of several generic and proprietary ARV formulations containing the non-nucleoside reverse transcriptase inhibitor nevirapine (NVP) as part of a pilot, quality assurance investigation. **Methods:** Tablets containing NVP (alone or in combination with other ARVs) were obtained from six international sources. NVP content of the six products was determined by HPLC. In total, six chromatographic analyses were performed for each individual tablet. **Results:** NVP content and demographic data for the individual products are listed in the table.

Trade Name (Manufacturer)	Country of Origin	Product Ingredients	NVP content (% CV)
Triomune 30 (Cipla)	Kenya	NVP 200 mg; d4T 30 mg; 3TC 150 mg	194.2 mg (3.1)
Viramune (Boehringer)	Lithuania	NVP 200 mg	201.9 mg (3.0)
Viramune (Boehringer)	S. Africa	NVP 200 mg	196.6 (2.2)
Triomune (Cipla)	Zambia	NVP 200 mg; d4T 40 mg; 3TC 150 mg	191.4 mg (2.1)
Nevimune (Cipla)	Zambia	NVP 200 mg	197.8 mg (3.0)
Nevirex (Aurobindo Pharma Ltd.)	Zambia	NVP 200 mg	205.5 (2.1)

The average NVP content among the tested preparations was 197.9 mg (coefficient of variation [CV] = 3.4%). Average accuracy of NVP content in tested preparations versus labeled amounts (200 mg) was 99.0%.

Conclusions: To our knowledge, this data represents the first publicly available account of drug content among generic ARV preparations. The results are encouraging and consistent with stringent manufacturing standards (± 3% of labeled drug amount). These data are reassuring given the widespread use of NVP-containing products in the developing world. Quality assurance analyses such as this one, must be conducted on a large-scale basis and include all generically available ARVs. When this information is available, health care providers and governmental agencies can determine which ARV formulations are most likely to provide HIV-infected patients in the developing world with the greatest possibility for clinical benefit.

INTRODUCTION

Although highly active antiretroviral therapy (HAART) has drammatically improved the prognosis of HIV-infected patients, 90% of infected individuals worldwide have no access to these medications.[1] Recently, coordinated efforts among interest groups, pharmaceutical manufacturers, and medical personnel have focused on providing antiretroviral access to HIV-infected patients in the developing world. Still, excessive drug costs continue to hamper the widespread availability of HAART. Fortunately, generic drugs are now available in many countries at costs that are considerably lower than discounted proprietary agents. However, recent reports of generic medications -including antiretrovirals- that contain little or no active ingredient, are disturbing.[2,3] Therefore, it is imperative that generic antiretroviral medications be analyzed for drug content and bioequivalency on a global basis. Moreover, these data must be made publicly available. We analyzed the content of several generic and proprietary antiretroviral formulations containing the non-nucleoside reverse transcriptase inhibitor nevirapine as part of a pilot, quality-assurance investigation.

METHODS

- Each nevirapine-containing tablet was individually weighed to determine the percentage of active ingredient before crushing to powder. Known quantities of tablet powder were weighed and dissolved in precise volumes of aqueous solvent. Each tablet master stock solution was injected onto an HPLC-UV photodiode array quantification system, and each single resulting chromatographic peak was analyzed for spectral purity.
- Library matching against a pure standard spectrum was performed; all data verifies chromatographic purity of the nevirapine peak in each solution. Specificity data on file also confirm non-interference from additional antiretrovirals contained in the multi-drug tablets.

METHODS *(Continued)*

- Calibration and quality control standards of known concentrations were prepared for quantitative analysis from nevirapine pure standard provided by Boehringer-Ingelheim. Serial dilutions of each tablet master stock solution provided two test concentrations for each tablet. HPLC analysis of each dilution was performed using a previously validated nevirapine assay. Multiple rounds of external proficiency testing have also verified the accuracy of this assay.
- Calculation of the concentration of each test solution, followed by consideration of all dilutions made from tablet to assay, resulted in accurate quantification of nevirapine in each of the six international tablets. In all, six chromatographic analyses were performed for each individual tablet.

RESULTS

Nevirapine content for each of the six tested preparations is shown in the table below. All nevirapine-containing products in this study were labeled as containing 200 mg of the drug. The average nevirapine content (average found mass) among the tested preparations was 197.9 mg (CV = 3.4%). Average accuracy of nevirapine content in the tested preparations versus labeled amounts was 99.0%.

Table. Nevirapine Products Analyzed for Drug Content

Product	Country where product was obtained	Date of manufacture (expiration)	Mean Nevirapine Content (cv [%])
Triomune 30 -Cipla Nevirapine 200 mg Stavudine 30 mg Lamivudine 150 mg	Kenya	Not provided (1/03)	194.2 mg (3.1)
Viramune -Boehringer Nevirapine 200 mg	Lithuania	Not provided Not provided	201.9 mg (3.0)
Viramune -Boehringer Nevirapine 200 mg	South Africa	Not provided (12/01)	196.6 mg (2.2)
Triomune 40 -Cipla Nevirapine 200 mg Lamivudine 150 mg Stavudine 40 mg	Zambia	12/01 (05/03)	191.4 mg (2.1)
Nevimune -Cipla Nevirapine 200 mg	Zambia	8/01 (07/03)	197.8 mg (3.0)
Nevirex -Aurobindo Pharma Ltd. Nevirapine 200 mg	Zambia	11/01 (10/03)	205.5 mg (2.1)

CONCLUSIONS

- To our knowledge, these data represent the first publicly available account of drug content among generic antiretroviral preparations.
- The results are encouraging and consistent with stringent manufacturing standards (± 3% of labeled drug amount); these data are particularly reassuring given the widespread use of nevirapine-containing products in the developing world.
- Studies documenting bioequivalence between generic and proprietary antiretroviral medications are also necessary. A recent investigation by the manufacturers of Triomune™ (Cipla) demonstrated bioequivalence between their single-tablet formulation of nevirapine, stavudine, and lamivudine and the same single-drug compounds produced by GlaxoSmithKline and Boehringer-Ingelheim.[4]
- Drug content analyses and bioequivalence studies must be conducted on a large-scale basis and include all generically available antiretrovirals. Such studies are currently in progress at NIH and UAB. When this information is publicly available, health care providers and governmental agencies can determine which antiretroviral formulations are most likely to provide HIV-infected patients in the developing world with the greatest possibility for clinical benefit.

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