Quality monitoring

Product information supplied with selected antiretrovirals in five African countries

WHO-prequalified antiretrovirals (ARVs) are widely used in HIV treatment programmes of Member States. For each prequalified medicine, a detailed WHO Public Assessment Reports (WHOPAR) is available on the WHO Prequalification website.

As part of a WHO quality monitoring study, the documents supplied with 107 samples of selected ARVs in five African countries were compared with the product information shown in the WHOPAR (for prequalified products) or publicly available information for the innovator product (for non-prequalified products). Deviations, some of them potentially impacting on patient safety, were found for most of the samples. It is recommended that regulators, procurers, health professionals and patients make more use of the WHOPARs to verify that the product information supplied with prequalified medicines conforms to that accepted by WHO.

Background

The product information accompanying a medicine is crucial to ensure its appropriate use. The aim of this study was to assess the content and readability of the product information accompanying selected ARV products in five African countries.

The study was conducted in the context of a quality monitoring survey of selected ARVs funded in large volumes by the Global Fund to Fight AIDS, Tuberculosis and Malaria.(1) The survey focused on paediatric formulations, medicines with five or more prequalified generics on the market, and products of which substandard or falsified versions had been reported to the WHO Global Surveillance System.

WHO prequalification is widely relied upon in procurement by UN-funded programmes and other international donors. For each prequalified medicine a detailed WHO Public Assessment Reports (WHOPAR) is published on the website of the Prequalification Team–Medicines (PQTm), including the approved product information for health professionals.

Authors: Dr Stephanie Buchholz¹, Dr Regine Lehnert², Dr Rutendo Kuwana³, Ms M Zweygarth⁴

¹ Independent expert
² External expert to WHO Prequalification Team
³ Technical Officer, WHO Technical Assistance and Laboratory Services
⁴ Contractor, WHO Essential Medicines and Health Products

RK coordinated the quality monitoring survey; RL contributed to the survey protocol. SB analyzed the product information. SB, RL and RK drafted the research report. MZ wrote the manuscript. We thank Dr Jitka Sabartova for her contributions to the main sample testing survey and for helpful comments on the manuscript.
and for patients (see Box 1). The WHOPARs are an extremely valuable resource for regulators and procurement organizations to verify the content of product information for prequalified medicines. They can also be used by health care professionals and patients looking for information about the medicines that they dispense and use.

**Methodology**

Samples of the ARVs selected for the survey\(^1\) were collected from September to November 2015 at 49 sites (national medicines stores, major dispensing facilities and treatment centres) in Burkina Faso, Rwanda, Nigeria, the Democratic Republic of the Congo and Zambia and sent to prequalified quality control laboratories for testing. At the laboratories the product information was extracted and forwarded to WHO for review. The medical content and structure of the product information supplied with prequalified products was compared with that shown in the WHOPAR. For non-prequalified products it was compared with the product information of the

<table>
<thead>
<tr>
<th>Product name</th>
<th>WHOPAR Part 3</th>
<th>WHOPAR Part 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine 50mg Dispersible Tablets</td>
<td>[Company name], HA###</td>
<td>[Company name], HA###</td>
</tr>
<tr>
<td>Patient Information Leaflet</td>
<td>July 2016</td>
<td>July 2016</td>
</tr>
<tr>
<td><em>Nevirapine 50mg Dispersible Tablets</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PATIENT INFORMATION LEAFLET</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[Product name]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Read all of this leaflet carefully before you start giving this medicine to your child.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Keep this leaflet. You may need to read it again.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• If you have any further questions, ask your healthcare provider.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• This medicine has been prescribed for your child. Do not pass it on to others. It may harm them, even if their signs of illness are the same as those of your child.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• If your child gets any side effects, talk to your healthcare provider. This includes any possible side effects not listed in this leaflet. See section 4.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product name</th>
<th>WHOPAR Part 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine 50mg Dispersible Tablets</td>
<td>[Company name], HA###</td>
</tr>
<tr>
<td>SUMMARY OF PRODUCT CHARACTERISTICS</td>
<td>July 2016</td>
</tr>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT</td>
<td></td>
</tr>
<tr>
<td>[Product name]</td>
<td></td>
</tr>
<tr>
<td>2 QUALITATIVE AND QUANTITATIVE COMPOSITION</td>
<td></td>
</tr>
<tr>
<td>Each dispersible tablet contains 50 mg of nevirapine (as anhydrous). Excipients with known effect: each tablet contains 41 mg of lactose monohydrate and 4.25 mg of aspartame (see section 4.4)</td>
<td></td>
</tr>
<tr>
<td>For a full list of excipients, see section 6.1.</td>
<td></td>
</tr>
<tr>
<td>3. PHARMACEUTICAL FORM</td>
<td></td>
</tr>
<tr>
<td>Dispersible tablet</td>
<td></td>
</tr>
<tr>
<td>White to off-white coloured, circular shaped, biconvex uncoated</td>
<td></td>
</tr>
</tbody>
</table>

---

\(^1\) Efavirenz (EFV) 600mg tablets (innovator product included on the WHO comparator list (2); Sustiva*)
- EFV/emtricitabine/tenofovir disoproxil fumarate 600/200/300mg tablets (innovator product: Atripla*)
- Lamivudine (3TC) 150mg or 300mg tablets (innovator product: Epivir*)
- Nevirapine (NVP) 50mg dispersible tablets
- 3TC/zidovudine (ZDV) 150/300mg

Overview of WHO Public Assessment Report (WHOPAR)

**HA### - Nevirapine - 50mg - Dispersible tablets - [Manufacturer name]**

Part 1 – Abstract
Part 2a – All accepted presentations
Part 2b – Visual appearance of the product
Part 3 – Patient Information Leaflet
Part 4 – Summary of Product Characteristics
Part 5 – Label
Part 6 – Discussion (status at the time of prequalification)
Part 7 – Steps before Prequalification
Part 8 – Steps following Prequalification

**Box 2: Product information available on the WHO Prequalification website**

https://extranet.who.int/prequal/key-resources/prequalification-reports/whopars
innovator product established on the WHO comparator list,\(^2\) if any (see footnote 1). The innovator product information was accessed from the EMA website.\(^2\)

As in a previous study (3) the following elements were compared: indications, dosing, contraindications, warnings, interactions, side effects, and pharmacological parameters (including mechanism of action, clinical efficacy, resistance, absorption and bioavailability, distribution, metabolism, elimination, pharmacokinetics in special populations and preclinical data).

The readability and usefulness of the patient information leaflets was assessed using adapted versions of the following tools:

- The Baker Able Leaflet Design (BALD) score (4) for good design characteristics in terms of text line length, fonts, titles, pictograms and boxes, use of positive (“do…”) rather than negative (“do not…”) advice, spacing, use of colour and paper quality; a score of 20–25 of 32 possible points was considered to reflect good layout and design;\(^5\)

- elements of the Ensuring of Quality of Information for the Patient (EQIP) score (6) relating to the document’s identification data (date of revision, manufacturer details, and any statement if and how patients were involved or consulted in the production of the leaflet) and structure (use of everyday language, use of generic medicine name, personal address to the reader, respectful tone, clear and balanced information, logical sequence, quality of graphs, figures and layout). Each applicable item was scored as being fully met (1 point), partly met (0.5 points) or not met (0 points), and the total was expressed as a percentage of possible points.

In addition, the sampling teams interviewed the staff at the sampling sites and asked them to complete two questionnaires. One served to explore the respondents’ perceptions of the completeness and usefulness of the product information supplied with ARVs, and sources of additional information. The other focused on the acceptability of dispersible ARVs.

**Results**

**Sample**

A total of 126 ARV samples were included in the survey. The samples originated from eight different manufacturers, all based in India. They represented:

- 21 prequalified products (98 samples);
- 6 products listed on the prequalification list based on U.S. FDA tentative approval (23 samples); and
- 2 products under WHO assessment at the time of the product information analysis (5 samples).

Product information for 121 samples was forwarded to WHO for analysis. In 14 cases this was for tentatively FDA-approved products that had no publicly available labelling information, and no corresponding innovator product was established on the WHO comparator list. The product information of 107 samples was therefore reviewed. For one prequalified product (five samples) the product information was mistakenly compared with that of the innovator product instead of the WHOPAR.

**Quality of product information**

**Structure**

Of the 107 sets of product information accompanying the samples
Quality monitoring

WHO Drug Information Vol. 32, No. 1, 2018

Product information supplied with selected ARVs in five African countries

- 51 had a WHOPAR-like structure, 14 of them included a PIL;
- 30 had a document titled “Prescribing information” with a PIL-like structure and some essential information for prescribers missing, none included a PIL;
- 17 had product information resembling the “Highlights of prescribing information” and “Patient counseling information” sections known from U.S. FDA-approved products, 4 included a PIL; and
- 9 had product information that did not fall into any of the above categories and was repetitive and/or very detailed, all included a PIL.

Readability and user-friendliness
The format and layout of the product information did not meet the criteria for easy readability: 24 of 107 documents reviewed were in font sizes much smaller than 8 points and could only be read with a magnifying glass. Some had very faint printing, which hampered reading additionally. The paper size of all except the PIL-like “Prescribing information” documents was too large (up to A2 format). A PIL was included in 28 of the documents, although none had a perforation line allowing to detach it. The BALD scores for the 28 PILs ranged from 7–15 out of 32, with a mean score of 9.8 and a median of 10. Thus none of the PILs met the BALD score considered acceptable in this study.

The EQIP criteria used in the study were only partly met. In all 28 PILs the generic name of the medicine was used. Most addressed the patient personally and presented information in a logical order. On the other hand, only 12 were written in easily understandable everyday language, only 13 had a revision date, and only 6 of these had been revised in the last seven years. Few presented balanced information on risks and benefits of medicines (see below). The mean EQIP score was 59.8% and the median score was 57%; only four PILs scored more than 64%.

Medical content
Of 107 SmPCs reviewed, 4 were fully in line with the information in the WHOPAR or the product information for the innovator product, 15 had minor deviations (for example because they included a different set of pharmacological parameters), and 88 had one or more substantial deviations.

Of the 107 samples, only 28 were accompanied by a PIL. Similarly as for the SmPCs, deviations from the WHOPAR or innovator product information were common in the PILs reviewed.

The numbers of deviations found in the different sections of the SmPCs and PILs are summarized in Figures 1 and 2.

Questionnaires

Sources and use of product information
In total, 51 questionnaires were completed by the sampling site staff – mainly pharmacists and clinicians – during interviews, and evaluated. Not all respondents answered all the questions. Additional statements were recorded in interviews conducted by the sampling teams.

Type of product information received:
The types of product information said to accompany most ARVs at the sampling sites differed from those observed in the study: 21 of 44 respondents said that they received a PIL alone (by this some may have meant the PIL-like “Prescribing information” seen in the study), 15 said both a PIL and an SmPC, and only 6 said that they received an SmPC alone.

Information for health professionals:
The most commonly used information
Medical content of product information: numbers of deviations found

**Figure 1:** Numbers of deviations found in summaries of product characteristics (SmPC)

<table>
<thead>
<tr>
<th>(n = 107)</th>
<th>In line with public information</th>
<th>Deviations</th>
<th>Major deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage *</td>
<td>19</td>
<td>2</td>
<td>86</td>
</tr>
<tr>
<td>Indication**</td>
<td>43</td>
<td>6</td>
<td>58</td>
</tr>
<tr>
<td>Interactions</td>
<td>16</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>Pharmacol. parameters</td>
<td>16</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>Warnings</td>
<td>41</td>
<td></td>
<td>66</td>
</tr>
<tr>
<td>Side effects</td>
<td>43</td>
<td></td>
<td>64</td>
</tr>
<tr>
<td>Contraindications</td>
<td></td>
<td></td>
<td>64</td>
</tr>
</tbody>
</table>

**Note:**
- Some samples had more than one type of major deviation

* Dosage, major deviations:
  - Missing additional dosage information (77 samples)
  - Missing weight band (27 samples)
  - Dosing for children included in products for adults (25 samples)
  - Wrongly assigned weight band (9 samples)
  - Wrong number of tablets (2 samples)

**Indications, major deviations:**
  - Inclusion of children in products for adults (30 samples),
  - Missing weight restriction (18 samples)
  - Exclusion of children (7 samples)
  - Wrongly assigned weight restriction (4 samples)

**Figure 2:** Numbers of deviations found in patient information leaflets (PIL)

<table>
<thead>
<tr>
<th>(n = 28)</th>
<th>In line with public information</th>
<th>Deviations</th>
<th>No PIL – 79 samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>4</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>7</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Precautions</td>
<td>13</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Contraindication</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Indication</td>
<td>19</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

sources were WHO or national treatment guidelines (44 respondents), the product information in the pack (30), the internet (13), and hospital formularies (7). Nineteen (19) respondents found the SmPCs in the product packs complete and sufficient for their needs, while 18 answered that they needed additional information. All except 2 respondents stated that they rarely or never accessed the WHO Prequalification website; one did not answer the question. WHOPARs were known to 15 respondents, 9 of whom stated that they had never used them.

**Information for patients:** The impact of the PIL on appropriate dosing and treatment compliance was rated as “crucial” by 25 respondents and as “minimal” by 22. While 20 respondents thought that the PIL provided sufficient information for patients, 25 did not think so; 17 felt that the PIL is of little use because it is not written in local language, and 3 mentioned that it is not
useful for illiterate patients. Dispensers in Burkina Faso said that some patients take only the tablets with them, leaving the product pack and the PIL behind at the facility to avoid stigmatization in the community.

Six respondents found the PILs difficult to read, 8 found the print too small, and 8 thought there was too much information. This is consistent with the low BALD scores found in the study.

Acceptability of dispersible ARV tablets for use in children
A total of 47 questionnaires were evaluated. Not all the respondents answered all the questions.

On the whole, the most frequently used dispersible ARV products as identified by the respondents were consistent with those sampled in the survey. Most respondents stated that they never or rarely received complaints about the taste, flavour or other aspects of dispersible ARVs.

While all except 4 respondents said that the instructions for dispersible products are easy to understand, their choices among four predefined definitions of “a small amount of liquid” in which to disperse the tablets varied widely: Less than 5 ml (5 respondents), 5–10 ml (19), 10–50 ml (5), and 50–100 ml (13). According to the WHOPARs, each tablet should be dispersed in 10 ml water.

Discussion
Despite the small sample size and some other limitations, this survey led to a better understanding of the quality, readability, format and use of the product information provided with ARV medicines in the African countries surveyed in this study. The results point to substantial shortcomings in terms of content and format.

Deviations from the medical information shown in WHOPARs or innovator product information were common. Some posed a direct risk for patient health. Thus, 30 of 107 SmPCs reviewed included a therapeutic indication and a dosage for children, although the prequalified or innovator product was recommended for use in adults only. This is concerning, as appropriate dosing for children cannot always be achieved with a dosage form and strength designed for adults. Two SmPCs of a paediatric ARV specified a higher dose for a specific weight band than that given in the WHOPAR, which could lead to potentially serious adverse effects. Information on dose adjustments and interactions – for example with contraceptives, antimalarials and herbal preparations – was missing in several cases, with a potential negative impact on treatment success and/or adherence. Less serious deviations pertained for example to missing therapeutic indications for adolescents and children. While this does not directly impact patient safety, it may restrict the treatment options for these patient groups.

Only 26% of the samples reviewed included a PIL, and the highest BALD score seen (15 points) was far below the score considered to represent good layout and design characteristics.

Less than 50% of the samples tested in the survey were registered in the country of use; the others were placed on the market through special permission mechanisms e.g. for donations or central supply to government centres. None of the NRAs of the surveyed countries was able to provide copies of the approved product information. In this study, different versions of the product information for the same medicine were seen in the same country. It therefore appears unlikely that the deviations
observed in the study were a result of national regulatory requirements.

The WHO survey team has communicated the findings to the regulators of participating countries and the manufacturers whose products were sampled in the study. The importance of complete and correct product information, and the possibility to verify this against publicly available WHOPARs, will be emphasized by WHO Prequalification Team in future interactions with stakeholders.

Conclusions and recommendations

Procurers and resource-constrained regulators rely on stringent assessment mechanisms, including WHO prequalification, to ensure that ARVs meet internationally accepted standards. This study found that the product information supplied with the sampled ARVs did not meet these standards.

Approving the product information supplied with medicinal products is a regulatory responsibility. However, buyers of medicines, health professionals and patients all have a role to play in making sure that the documentation supplied with products is complete and correct. Rapid action should be taken to increase the awareness and use of WHOPAR information by regulators, procurers, health professionals and patients. The development of a Prequalification App for mobile phones may be considered. Such a PQ-App would allow the easy selection of all WHOPARs available, with key features like dosing, therapeutic indications and contraindications displayed directly on the mobile phone.

In addition, manufacturers and regulators should be sensitized to the requirements for leaflet design and formatting to ensure that the product information is understood by health professionals and patients.

References