FIFARMA
Federación Latinoamericana de la Industria Farmacéutica

Examples of Patient Safety Issues with Pooled Procurement

This is not a "leave-behind"

- We are aware of at least two examples where patient safety was placed at risk, both resulting from the pooled procurement of darunavir by the Panamerican Health Organization (PAHO) in 2016 - one in Chile and one in Brazil - other examples may exist outside our direct knowledge:
    - In 2016 following a joint negotiation by Mercosur's Ad Hoc Committee for High Costs Medicines, PAHO started to supply darunavir copy (HIV/ARV drug) to approximately 8 countries in LATAM. In at least two of these countries (Brazil and Chile) the innovator drug was replaced from one day to the next by the copy and in both countries the copy was not approved by local regulatory agencies and did not comply with local regulatory requirements **(1).**
    - In both cases, a large number of patients (~2K patients) had their medications switched from the originator to the copy without their previous knowledge and their doctor consent.
    - In both cases, the darunavir copy was supplied from an Indian manufacturer without any local presence or representation in country.

- On November 24, 2018, we learned via official statements of Mercosur, that member countries decided to join demand to pool procure a drug called tacrolimus, using PAHO's strategic fund. While this drug had been on the strategic fund list for some time, it appears that the use of this mechanism to acquire the drug had been limited and now it will be expanded. Tacrolimus is a life-saving drug, an immunosuppressant prescribed to some of the most vulnerable patients: patients that have received organ transplant (kidney, liver, heart). These patients depend on this drug and need to take it for their entire life after a transplant.

- Even though tacrolimus is an off-patent drug, with multiple generic manufactures currently supplying the product, our concerns are the same as those expressed in the darunavir case, hence our motivation to raise our concerns regarding patient safety issues with HHS:
    - How is supply integrity going to be assured by PAHO and Mercosur member countries? Currently, tacrolimus is supplied by many locally-based manufacturers, with locally registered tacrolimus. Supply issues have happened before in the region* and were resolved only because other manufacturers were available locally. What will happen if PAHO starts to procure tacrolimus from single generic source? How will it ensure reliability of supply? If there are supply disruptions and no more incentive for locally sourced manufacturers to remain in the market, what will be the plan B for patients that

depend on this drug to survive?

- How will local regulatory standards be ensured? Locally sourced products currently available in the region comply with local sanitary regulations, including post-market surveillance, local patient and physician support (customer service/ 1-800), appropriate labeling/packaging, stability requirement etc… what we experienced in the darunavir case (and we fear may happen with tacrolimus) is that products purchased via PAHO did not comply with the same standards. While it is true that some important aspects of quality assurance are covered via the pre-qualification process, this simplified process was not created to substitute product registration in countries with fully functioning regulatory agencies – as is the case with LATAM countries.

- How will patients stable under their current tacrolimus drug be assured that they can remain in their current medication? Transplanted patients taking tacrolimus are very complex patients, changing their medications is a risk that is difficult to justify. For this reason, in Panama for instance, tacrolimus is included in a positive non-switch list. In the case of darunavir, ~2K patients were switched without warning or voices to a darunavir copy that was not approved under local regulatory standards – what will happen with theses transplant patients taking tacrolimus? **(2)**

(1)
Darunavir Example - Brazil

- *An internal PhRMA member analysis of the secondary packaging and product insert of the copy, unregistered, darunavir product acquired via PAHO showed several discrepancies versus local regulatory standards in Brazil, specifically:*
  - *The unregistered product's packaging insert did not match local ANVISA requirements in 25 areas including:*
    - *Discrepancies in product indication for pediatric patients and for naïve patients, including non-approved indication*
    - *Absence of technical responsible and call center number/local contact information*
    - *Storage requirements non-conforming with Brazilian regulation for determining stability conditions*
    - *Absence of multiple required warning language and patient recommendations language required by Brazilian regulation*
  - *Additionally, the unregistered product's secondary packaging did not match local ANVISA requirements in 17 areas including:*
    - *Absence of warning that product is part of a specially controlled group of drugs, commanding special distribution rules*
    - *Storage requirements non-conforming with Brazilian regulation for determining stability conditions*
    - *Absence of technical responsible and call center number/local contact information*
    - *Absence of required warning language and patient recommendation language required by Brazilian regulation*
    - *Lot, expiration date and date of manufacturing in discordance with local regulation*

Darunavir Example - Chile

- *Chile joined the same procurement process as Brazil for Darunavir and proceeded to procure the generic version of the product without local regulatory approval by the local sanitary authorities, the ISP.*
- *Local regulation in Chile requires that CENABAST only procure products with local sanitary registration for the National Programs and, under very narrow and exceptional circumstances, CENABAST is permitted to acquire products without*

such sanitary approval. Exceptional circumstances include, according to the sanitary code, cases of "supply shortages and inaccessibility" of the product – clearly not the case of darunavir, always supplied correctly by the innovator company Chile for many years.

- *Even under exceptional circumstances for importation without local regulatory approval, a provisional license would need to have been issued by ISP. Also, according to local regulations, the product imported should have been submitted to processes to "adapt it to the local regulations", including "packaging, safety seals and quality controls" – processes that never took place in this case.*
- *At least 3 hospitals that received the product without local registration: Hospital Regional de Rancagua, Hospital Nacional Puerto Montt and Hospital Clinico de la Universidad de Chile Jose Joaquin Aguire. Sample of Darunavir without local regulatory approval were collected in at least one of these hospitals and have shown that the products were not submitted to local adaptation and quality inspection.*
- *Among the most visible infractions internal assessment identified that the product imported in Chile from via PAHO without local regulatory approval, was the labeling of the products by CENASBAST as "Bioequivalent", a claim for which no evidence was provided. For a product to be classified as "Bioequivalent", appropriate evidence of the clinical therapeutic properties with the originator product should have been provided and approved by ISP.*

(2)

Label:

- *Tacrolimus is indicated for[1]:*
  - *Prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants*
  - *Use concomitantly with adrenal corticosteroids; in kidney and heart transplant, use in conjunction with azathioprine or mycophenolate mofetil*
- *Based on narrow therapeutic index for Tacrolimus and the complexity of the patients on these indications, the treatment with this drug needs a close monitoring of whole blood trough concentration and drug related events1.*

Medical Information:

- *All indications for Tacrolimus represents complex clinical situations for patients and healthcare systems, related with high investment on resources[2].*
- *Several professional transplant societies have generated skepticism of the generic switching process for this drug based on narrow therapeutic index[2].*
- *Even though some publications exist on medical switching for some generics (no innovator), well-designed, controlled prospective studies testing the validity of the regulatory bioequivalence testing approach for narrow therapeutic index immunosuppressants in transplant recipients have been lacking3.*
- *Failure on proper effect of this class of drug represents an important risk for patients due a complexity and severity of these conditions.*

Conclusions:

- *Close monitoring of Drug related events and pharmacovigilance (PV) are key steps on treatment with Tacrolimus.*
- *Access to this drug should guarantee product quality and support from a robust PV system close of HCPs responsible for the treatment.*

References:

1- *FDA Label - Prograf (https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050709s031lbl.pdf)*
2- *J Med Econ. 2018 Nov;21(11):1067-1074. (https://www.ncbi.nlm.nih.gov/pubmed/30032686)*
3- *PLoS Med. 2017 Nov 14;14(11):e1002428 (https://www.ncbi.nlm.nih.gov/pubmed/29135993)*

- ***** *In Mexico, the 2018 Consolidated Tender was divided in 2 distributors Pihcsa (80% of the contract) and Landsteiner (20%, of the contract), Pihcsa was unable to deliver Tacrolimus and the government had to resort to an alternative supplier.*