Supporting Sustained Supply through the Coordinated Procurement of ARVs

ARV Procurement Working Group Newsletter

April 2018

Introduction

Through quarterly order cycles and business calls, the APWG has continued to support the ARV market in low- and middle-income countries (LMIC) via coordinated procurement, strategically managed demand, and reduced fragmentation. As a supplement to our routine work, the APWG publishes a biannual newsletter that provides an update on some of the key topics and issues facing the ARV market.

Within the April 2018 edition of the APWG newsletter: TLD supply security, supply and demand of LPV/r (40/10 mg) solid formulations, APWG webinars to the field, and pipeline optimal ARVs.

Recommendations on Country Procurement during the Transition to TLD

The generic ARV market will be in a state of transition in 2018 with the introduction of a new fixed-dose combination (FDC) to serve as a first-line treatment option for adults. The product, known as 'TLD', is a single tablet comprised of tenofovir disoproxil fumarate 300 mg (TDF), lamivudine 300 mg (3TC), and dolutegravir 50 mg (DTG). Demand for TLD is expected to be significant; the APWG, in coordination with donors, various procurement agents, and other partners, has compiled key recommendations for procurement of TLD to help country programs adequately prepare for the transition. Ultimately, the goal is to ensure all patients, both new and existing, have access to a sustainable supply of ARVs before, during, and after the transition to TLD, while limiting the amount of wasted legacy ARV stock, providing flexibility in county supply plans, and avoiding a disruption to the market.

The APWG published a memo in February providing recommendations to country teams on procurement during the transition to TLD. To ensure supply security during the transition to TLD, the APWG recommends country programs:

- **Plan orders with as much advance notice as possible to procurement agents and suppliers.** Lead times will be slightly longer during the first stage of transition as manufacturers refine their processes for manufacturing TLD but are expected to normalize as steady-state production is reached. Preferably notify procurement agents 6-12 months in advance.
- **Stagger large TLD orders into smaller deliveries to avoid overburdening the system.** To avoid overburdening suppliers with one single order representing a very significant volume, the APWG recommends orders be staggered across many smaller deliveries. Smaller orders keep the manufacturers operating consistently and efficiently so as to better meet needs.
- **Share 12-18 month procurement plans for TLD with the APWG and partners.** Country-level procurement plans, that include the TLD transition and beyond, will help the APWG put together a global overview of TLD demand to map against existing supply capacity. For example, procurement planning as a result of USAID's COP process will help inform the likely ordering for 20+ high volume countries.
- **Ensure sufficient buffer stock throughout the transition and beyond.** TLD roll-out should begin once there is sufficient buffer stock built-out nationally. Countries should additionally try to phase-in TLD at rates that will minimize wastage of legacy first-line adult products.

Update on TLD Capacity

Mylan recently received FDA approval for a process variation that allows them to increase their TLD production capacity. Deliveries scheduled for March and April may be slightly delayed, as this approval came later than anticipated; however, all orders and requests for the rest of the year known to the APWG at the time of this publication should not be impacted based on production capacity information provided by both suppliers. The APWG continues to be in close contact with the suppliers to share and monitor demand and capacity figures, and will provide insight and advice related any emerging supply demand risks. At this time, the APWG continues to recommend that new orders and requests be placed with as much advance notice as possible, and believes there is sufficient capacity to meet current demand.

Update on the Supply and Demand of LPV/r (40/10 mg) Solid Formulations

Looking ahead, demand for LPV/r oral pellets is expected to continue to exceed Cipla's monthly production capacity for the product. As such, the APWG will continue to connect with Cipla to discuss the latest demand and share updates on lead times and target deliveries in order to mitigate any potential supply issues.

In February, Cipla filed a process variation with the USFDA that, if approved, would allow the monthly manufacturing capacity to increase to ~50K packs/month. Approval of this variation is expected in the latter half of 2018.

Additionally, Mylan has developed a LPV/r (40/10mg) granule product that may serve as another alternative to oral solution for children. Mylan has filed the granule product with the USFDA and WHO PQ with approvals expected in the latter half of the 2018. Differences between granules and pellets are relevant; granules will be supplied in sachets, whereas pellets are supplied in capsules. It is also important to note the differences between administration of granules and pellets. The APWG recommends that programs recognize the differences in implementation, consider adopting only one product (whether granules or pellets) in order to avoid confusion at facilities, and ensure there is relevant planning and discussions with procurement agents.

The APWG's guidance on paediatric LPV/r products from last year remains valid today and the group continues to recommend programs hold off any large scale-up or transition plans until there is security in the supply. Lead times are still expected to be long; thus, the APWG recommends that programs place orders with as much advance notice as possible and build in buffer time for expected deliveries.

APWG Webinars on Optimal ARVs

In February, the APWG hosted two webinars that focused on current and pipeline optimal ARVs:

- **'Introduction to New Optimal ARVs'**, the first webinar, provided key clinical considerations and guidance on optimal adult and paediatric drugs. Many products were included in the discussion such as adult and paediatric DTG, low-dose efavirenz (EFV400), LPV/r oral pellets, and paediatric raltegravir (RAL). Beyond the clinical overviews, the webinar also focused on general market-wide updates on the development and availability of optimal ARVs.
- **'Country Decision Making and Supply Considerations for New Optimal ARVs'**, the second webinar, focused on supply planning and gave an overview of the resources of support for country programs.
- Recordings of the two webinars will be made available online.

While the first two webinars focused on primarily on sub-Saharan Africa, the APWG plans to repeat the webinars on different dates and times for other regions, with versions in English, French, and Spanish.

Optimal ARVs in Development Expected to Launch in the ARV Market

As covered in the APWG webinars, a number of optimal ARVs are in development or have recently become SRA approved and are expected to launch in the ARV market in the quarters ahead. They include:

- **Paediatric '4in1'.** DNDi has been collaborating with Cipla on the development of an FDC of ABC/3TC/LPV/r, which is the preferred 1L regimen for infants and young children ages 3 or less. The product will be in the form of granules and Cipla plans to file towards the end of this year.
- **Paediatric ABC/3TC/EFV.** The WHO currently recommends ABC/3TC/EFV as the preferred first-line treatment for children between the ages of 3 and 10. Three manufacturers are in the final stages of development of a generic FDC of ABC/3TC/EFV (150/75/150mg). The first SRA filing is expected in Q4 2018.
- **Paediatric DTG.** CHAI, through the Unitaid Optimal ARV Project, released an RFP in November 2017 to generic manufacturer(s) to partner with for accelerated development of paediatric DTG. The incentive will allow an accelerated development timeline to address lags between regulatory approval of an innovator and product launch by generic supplier. The incentive is being offered to partially offset the cost for developing generic DTG 10mg scored dispersible.
- **DRV/r Adult FDC.** CHAI, through the Unitaid Optimal ARV Project, similarly released an RFP in December 2017 to accelerate affordability of a darunavir/ritonavir (DRV/r) 400/50mg formulation. The goal of the project is to rapidly enable the launch of an SRA-approved product that is affordably prices so that patients in LMICs will finally have access to the optimal protease-inhibitor option.
- **TAF/FTC/DTG Adult FDC.** The USFDA tentatively approved Mylan's TAF/FTC/DTG (25/200/50mg) product in February. Please note that TAF is currently not recommended by the WHO guidelines and complete data on TAF use during pregnancy and TB-treatment for guidelines consideration is expected to be available by 2020.

Quarterly Order Cycle Coordination

The APWG Procurement Consortium consolidates the orders of ARVs around fixed quarterly order cycle dates. These dates have been agreed upon by the AWPG and shared with suppliers and other stakeholders.

The aggregation of orders for at-risk ARVs (i.e., low-volume paediatric and adult products as well as those ARVs in transition) around this schedule allows manufacturers to plan production accordingly. Furthermore, consolidated product orders are more likely to meet the required minimum batch size and thus potentially avoid extended lead times associated with sub-batch orders.

Countries procuring ARVs independently or through non-APWG procurement agents are encouraged to use the quarterly order dates below to ensure a reliable supply of paediatric ARVs.

Deadline For Orders To Be Placed With Suppliers*	
Q1 2018	**30 March 2018**
Q2 2018	**29 June 2018**
Q3 2018	**28 September 2018**
Q4 2018	**28 December 2018**
*Orders should be submitted to procurement agents at least 6 weeks before these dates	

Scheduled ordering four times a year is especially recommended for low volume paediatric and adult ARVs, a list of these prioritised products is provided:

Prioritised Paediatric ARVs (2016 IATT status)	
Optimal	ABC/3TC (120/60mg) dispersible
	LPV/r (80/20mg/ml) solution
	LPV/r (40/10mg) oral pellets
	NVP (50mg) dispersible
Limited-Use	3TC (50mg/5ml) solution (100ml)
	ABC (60mg) dispersible
	ATV (100mg)
	AZT (60mg) dispersible
	AZT (50mg/5ml) solution (100ml)
	RTV (25mg) tablets
Non-Essential	ATV 150mg
	AZT (50mg/5ml) solution (240ml)

Prioritised Adult ARVS
ABC 300mg
ATV 300mg
AZT 300mg
DRV 400mg
DTG 50mg and FDCs
EFV 400mg FDCs
RAL 400mg
RTV 100mg
TDF 300mg
3TC 150mg

New Product Availability

The following optimal and limited-use paediatric products as well as adult formulations have been either tentatively approved by the USFDA, received WHO Prequalification (PQ), or have been reviewed and approved by the Global Fund Expert Review Panel since the publication of the last APWG Newsletter.

Latest SRA Approvals			
Product	**Patient Type**	**Supplier**	**Approval Body**
ABC (60mg) Tablet (Disp & Scored)	Peds – Lim. Use	Micro Labs	FDA
ABC/3TC (600/300mg) Tablet	Adult	Hetero	WHO PQ
ATV/r (300/100mg) Tablet	Adult	Cipla	FDA
DTG (50mg) Tablet	Adult	Cipla	FDA
DTG (50mg) Tablet	Adult	Cipla	WHO PQ
DTG (50mg) Tablet	Adult	Emcure	ERP
DTG (50mg) Tablet	Adult	Hetero	ERP
EFV (200mg) Tablet (Scored)	Peds – Optimal	Micro Labs	FDA
EFV (600mg) Tablet	Adult	Shanghai Desano	WHO PQ
EFV (600mg) Tablet	Adult	Micro Labs	WHO PQ
RAL (600mg) Tablet	Adult	Merck	FDA
TAF/FTC/DTG (25/200/50mg) Tablet	Adult	Mylan	FDA
TDF (300mg) Tablet	Adult	Laurus Labs	FDA
TDF/3TC (300/300mg) Tablet	Adult	Micro Labs	FDA

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APPENDIX: The 2016 IATT Paediatric ARV Formulary and Limited-use List

2016 IATT Optimal Formulary			
Drug Class	**Drug**	**Formulation**	**Dose**
NNRTI	EFV	Tablet (scored)	200mg
NNRTI	NVP	Tablet (disp. scored)	50mg
NNRTI	NVP	Oral liquid	50mg/ml, 100ml
PI	LPV/r	Tablet (heat stable)	100/25mg
PI	LPV/r	Oral liquid	80/20mg/ml
PI	LPV/r	Oral pellets	40/10mg
FDC	AZT/3TC	Tablet (disp. scored)	60/30mg
FDC	ABC/3TC	Tablet (disp. Scored)	60/30mg, 120/60mg
INSTI	RAL	Chewable tablet	100mg

2016 IATT Limited-Use List				
Drug Class	**Drug**	**Formulation**	**Dose**	**Rationale For Use**
NRTI	AZT	Oral liquid	50mg/ml -100ml	Infant prophylaxis or as part of neonatal treatment regimen
NRTI	3TC	Oral liquid	50/5mg/ml	Neonatal treatment regimen
NRTI	ABC	Tablet (disp. scored)	60mg	Children <3 years undergoing TB treatment requirement triple nucleoside regimen
NRTI	AZT	Tablet (disp. scored)	60mg	Children <3 years undergoing TB treatment requirement triple nucleoside regimen
PI	DRV	Tablet	75mg	Third line
PI	RTV	Tablet	25mg	Boosting of noncoformulated PIs (DRV and ATV)
PI	RTV	Oral liquid	400/5mg/ml	Super boosting of LPV/r during TB treatment
PI	ATV	Solid oral dosage form	100mg	Alternative second-line
INSTI	RAL	Tablet (chewable, scored)	25mg	Second-line after LPV/r –containing first-line failure
FDC	AZT/3TC/NVP	Tablet (disp. scored)	60/30/50mg	Alternative first-line

For more details on the revised IATT list, please contact Martina Penazatto (penazzatom@who.int), Nandita Sugandhi (nss14@cumc.columbia.edu), Wesley Kreft (wkreft@nl.pfscm.org), or Christine Malati (cmalati@usaid.gov).