POLICY BRIEF

SUPPLY PLANNING FOR NEW DOSAGE FORM OF LOPINAVIR AND RITONAVIR ORAL PELLETS

40MG/10MG per capsule, pack of 120 capsules

World Health Organization

IATT
THE INTERAGENCY TASK TEAM
The Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children

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This policy brief provides antiretroviral therapy (ART) programme managers, implementing partners, procurement and supply chain managers, and other relevant stakeholders with key points to consider before and during the introduction of the new dosage form of ritonavir-boosted lopinavir (LPV/r) oral pellets. The pellets are packaged into capsules with each capsule containing the equivalent of 40mg of LPV and 10mg of ritonavir. The LPV/r pellet[1] dosage form can be sprinkled on soft food or given with breastmilk or formula. It is hoped that the new dosage form will address some of the long standing challenges presented by use of the currently available paediatric dosage forms of LPV/r.[2]

For countries deciding to include LPV/r pellets in their national guidelines for the treatment of HIV-infected infants and young children, it is important to take a coordinated approach to the introduction of this product in order to support a reliable supply chain with timely and appropriate uptake at the patient-level.

The information contained herein does not replace that provided with the product, as approved by the regulatory authority. Practitioners are encouraged to read the approved product package insert and relevant treatment guidelines for more detailed and up-to-date information.[3]

BACKGROUND

In 2013, WHO recommended either abacavir (ABC) or zidovudine (AZT) with lamivudine (3TC) and LPV/r as first-line ART for all HIV infected infants and children under 3 years of age.[4]

Until recently the only available paediatric dosage forms of LPV/r included an oral liquid (80mg/10mg /ml) that requires cold chain transport and storage until the point of dispensing, and heat-stable tablets (100mg/25mg) that must be swallowed whole and cannot be chewed, crushed or dissolved in liquid.

On May 21, 2015, LPV/r 40mg/10mg heat-stable oral pellets (in a capsule) received tentative approval by the United States Food and Drug Administration (USFDA) for use in children above 14 days of age and ≥5kg.[5] This unique formulation will require proper sensitization and training for healthcare workers and caretakers to be administered appropriately.

[1] This formulation has been referred to as a "sprinkle" or "mini-tab" in past references.
[2] **LPV/r oral liquid** contains 42% ethanol and 15% propylene glycol and has an unpleasant taste. It is NOT heat stable and requires cold chain transport and storage at 2°C-8°C. LPV/r oral liquid should be kept at 2°C-8°C at least up to the point of dispensing. Outside the refrigerator, LPV/r oral liquid is stable at 25°C for 42 days (6 weeks). LPV/r oral liquid should be taken with food. **LPV/r heat-stable tablets** MUST be swallowed whole and MUST NOT be broken, crushed, chewed or dissolved before administration. LPV/r tablets can be taken with or without food and are suitable for children ≥10kg who are able to swallow tablets whole.
[3] Further guidance for health care workers, care-givers, and implementing partners is available in the FACT SHEET ON LOPINAVIR AND RITONIVIR (LPV/r) ORAL PELLETS 40MG/10MG PER CAPSULE POLICY BRIEF
[4] http://www.who.int/hiv/pub/guidelines/arv2013/en/index.html
[5] The USFDA has approved the use of pellets in children ≥5kg though the safety of dosing in infants 3-4.9 kg has been demonstrated in a small number of infants in CHAPAS-2.

IMPORTANT PROGRAM CONSIDERATIONS FOR LPV/R USAGE IN INFANTS AND YOUNG CHILDREN

Recommendations for National Program for Introduction of LPV/r Oral Pellets

1. National program stakeholders must agree to include the LPV/r pellet formulation in their procurement list and appropriate dosing guidance in National Treatment Guidelines for the target patient population, including age groups and weight bands.
2. Stakeholders should map the approach and timelines for the introduction of the product into clinical use. Guidelines should advise whether the LPV/r pellets should only be considered for newly initiated patients and/or whether to switch children less than 3 years of age who are currently doing well on NVP-containing regimens or other LPV/r formulations.
3. National program plans may wish to recommend either a gradual phase-in, pilot for the LPV/r pellets or a country-wide scale-up.
4. Country-specific processes, such as product registration must be in place to facilitate importation of LPV/r pellets.
5. Decisions must be communicated to stakeholders, including health care workers and procurement staff.

PLANNING FOR THE INTRODUCTION OF LPV/R ORAL PELLETS INTO THE NATIONAL PROGRAM

Convene a representative cross-functional, multi-stakeholder working group of implementers, pharmacists, supply chain and procurement staff and funders (local and international, as appropriate) or use an existing, appropriately constituted Working Group to make decisions on the following issues:

1. Determine the ARV regimens in use for each age group below:
   - Breastfeeding or formula fed infants (0 - 6 months)
   - Infants and young children 6 months - 3 years
   - Children >3 years

2. Determine the type and quantities of LPV/r formulations needed for each age group. Critical points to consider are included in the table below:

DISCUSSION POINTS	PROGRAM DECISION
Will the introduction of the LPV/r pellet increase current uptake of LPV/r for first-line regimens?	
Will the introduction of LPV/r pellets increase the number of children on treatment? If so, is there a scale-up plan that can be used to quantify the projected demand?	
Will LPV/r oral liquid and/or LPV/r 100mg/25mg heat-stable tablets continue to be available? If so, for which group of patients will they be used and in what quantities?	
How many patients are expected to switch from other LPV/r formulations to LPV/r pellets? When is the switch planned to start? Over what time period will this switch be made?	
How many patients are expected to switch from NNRTI-containing regimens to LPV/r- based regimens using the pellets? When is the switch planned to start? Over what time period will this switch be made?	
What quantity of the LPV/r oral liquid, 100mg/25mg, or other NNRTI-containing regimens are in stock in the entire supply pipeline? How much is on order? Can these orders be adjusted or cancelled, if necessary?	
Will the introduction of LPV/r pellets lead to wastage of existing stocks of LPV/r oral solution, 100mg/25mg tablets or other drugs? If so, what is the value of the stock? Can these be written off? If not, factor in the timeline to consume this stock before introduction of LPV/r pellets.	

3. Plan health care worker training on appropriate prescribing and administration of LPV/r pellets. Further guidance for health care workers, caregivers and implementing partners is now available through the Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children (IATT) website.[6]

4. Prepare revised budgets taking into account the proposed changes above; cost of product, programmatic costs, product sensitization and training materials, and supply chain costs (including write-offs if deemed necessary).

5. Ensure demand visibility by monitoring uptake and making adjustments based on demand signals.

6. Develop and communicate the implementation plan.

[6] FACT SHEET ON LOPINAVIR AND RITONIVIR (LPV/r) ORAL PELLETS 40MG/10MG PER CAPSULE POLICY BRIEF

Based on the decisions of the Working Group, procurement managers can apply estimated patient numbers, timing of introduction, and the likely scale-up of patients on LPV/r containing regimens, including those being transitioned to or starting treatment on the LPV/r pellets, to create new demand forecasts across all pediatric formulations in use in the country. With the revised demand, forecast procurement managers can then compare the demand to existing stocks and outstanding orders to prepare new orders, including LPV/r pellets. It is recommended that initial LPV/r pellet orders include sufficient buffer stock to account for unpredictable uptake during the introduction phase.

A dosing chart is included in the table below for quantification of LPV/r formulation requirements by weight band.

SIMPLIFIED WEIGHT BAND DOSING SCHEDULE FOR LPV/r oral pellets 40mg/10mg, oral liquid 80mg/20mg/ml, and heat-stable tablets 100mg/25mg

WEIGHT BAND (KG)	NUMBER OF LPV/R ORAL PELLETS 40MG/10MG CAPSULES		LPV/R 80MG/20MG/ML ORAL LIQUID		NUMBER OF LPV/R 100MG/25MG TABLETS	
	AM	PM	AM	PM	AM	PM
3-4.9 kg[7]	2	2	1ml	1ml	NR	NR
5 - 5.9kg	2	2	1 ml	1 ml	NR	NR
6 - 9.9kg	3	3	1.5ml	1.5ml	NR	NR
10 - 13.9kg	4	4	2ml	2ml	2	1
14 - 19.9kg	5	5	2.5ml	2.5ml	2	2
20 - 24.9kg	6	6	3ml	3ml	2	2
25 - 29.9kg	7	7	NR	NR	3	3
30 - 34.9 kg	8	8	NR	NR	3	3

NR=NOT RECOMMENDED

Adapted from Cipla package insert approved by USFDA and WHO 2013 simplified dosing of child-friendly solid and oral liquids for twice daily dosing.[8]

[7] The USFDA has approved the use of pellets in children ≥5kg though the safety of dosing infants 3-4.9 kg has been demonstrated in a small number of infants in CHAPAS-2. The pellets may be administered in this weight band if infants are developmentally able to swallow them.
[8] http://www.who.int/hiv/pub/guidelines/arv2013/annexes/WHO_CG_annex_7.pdf

PRODUCT INFORMATION FOR LPV/R 40MG/10MG HEAT STABLE ORAL PELLETS

1. USFDA tentative approval received on May 21, 2015.
2. Commercial pack size is 120 capsules/pack, in high density polyethylene (HDPE) bottles.
3. Shelf life is 24 months when stored below 30°C.
4. The price per pack of 120 capsules is $ 19.20/pack ex-works as of June 2015. The projected cost savings in using the pellets relates to elimination of cold chain requirements during transport and storage that is now associated with the LPV/r oral liquid and reduced weight and volume of pellets compared to oral liquid. Procurement personnel can help to calculate total landed cost of each product for comparison.
5. LPV/r oral pellets are expected to be available for procurement by Q4 of 2015. Lead times will be determined by the number of orders pending with the supplier. Countries are advised to start the procurement process so that firm orders are with the supplier as soon as possible.
6. Kindly contact the interagency Paediatric ARV Procurement Working Group (PAPWG) at the earliest opportunity for up to date supply availability information. For other information, including clinical or national policy decisions, contact the Optimal Formulary Sub-Committee of the IATT.

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