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FACT SHEET

ON LOPINAVIR AND RITONAVIR (LPV/R) ORAL PELLETS

40MG/10MG per capsule
bottle pack containing 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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In response to a longstanding demand for a heat-stable and easy to administer formulation of ritonavir boosted lopinavir (LPV/r) for infants and young children, a new formulation in pellet[1] form is now available.

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.

BACKGROUND

In 2013, WHO recommended either abacavir (ABC) or zidovudine (AZT) with lamivudine (3TC) and LPV/r as first line antiretroviral therapy (ART) for all HIV-infected infants and children between 14 days and 3 years of age.[2]

There are challenges with both of the currently available dosage forms of LPV/r for this age group:

- LPV/r 80mg/20mg/ml oral liquid is supplied in a pack of 5 bottles each containing 60ml or one bottle containing 160ml. This formulation contains 42% ethanol and 15% propylene glycol and has an unpleasant taste. It is **NOT** heat stable and requires cold chain transport. LPV/r oral liquid should be kept at 2˚C-8˚C at least up to the point of dispensing. Once dispensed and 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 100mg/25mg heat-stable tablets in packs of 60 tablets and 120 tablets are formulated in a "melt extrusion" matrix, meaning that they **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. These tablets are NOT suitable for infants or younger children that are unable to swallow tablets whole.

[1] This formulation has been referred to as a "sprinkle" or "mini-tab" in past references.
[2] World Health Organization. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.* Recommendations for a public health approach June 2013. http://www.who.int/hiv/pub/guidelines/arv2013/en/index.html

NEW DOSAGE FORM: LOPINAVIR AND RITONAVIR ORAL PELLETS 40MG/10MG PER CAPSULE

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.[3]

The CHAPAS 2 Trial[4,5] was an open-label, randomized control crossover trial of the LPV/r 40mg/10mg oral pellets, 80mg/20mg/ml oral liquid, and 100mg/25mg tablets in Ugandan infants and children ages 3 months to < 13 years old and found that LPV/r oral pellets provided similar therapeutic levels to both oral liquid and tablets when taken with food.

This **FACT SHEET** provides simplified information to facilitate proper dosing and administration of lopinavir and ritonavir 40mg/10mg oral pellets.

INDICATIONS

LPV/r oral pellets 40mg/10mg per capsule is indicated for the treatment of HIV-1 infection in infants and children 14 days of age and older and ≥ 5kg[6] in combination with other antiretroviral agents.

LPV/r oral pellets 40mg/10mg should not be administered to premature neonates (born one month or more before expected date of delivery) until 14 days after their due date.

SIMPLIFIED WEIGHT BAND DOSING SCHEDULE FOR LPV/R oral pellets 40mg/10mg

LPV/r oral pellets are administered twice daily (every 12 hours). LPV/r **SHOULD NOT** be administered once daily (every 24 hours) to children <18 years of age.

WEIGHT BAND (KG)	CAPSULES OF 40MG/10MG LPV/R ORAL PELLETS, TWICE DAILY	
	AM	PM
3-4.9kg[6]	2	2
5-5.9kg	2	2
6 - 9.9kg	3	3
10- 13.9kg	4	4
14 - 19.9kg	5	5
20 - 24.9kg	6	6
25 - 29.9kg	7	7
30 - 34.9 kg	8	8
≥ 35kg[7]	10	10

Adapted from Cipla package insert approved by USFDA and WHO 2013 dosages of recommended antiretroviral drugs

[3] 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.
[4] Musiime, V. et al. 'The Pharmacokinetics and Acceptability of Lopinavir/Ritonavir Minitab Sprinkles, Tablets, and Syrups in African HIV-Infected Children.' *J Acquir Immune Defic Syndr*. 2014 Jun 1. 66(2) 148-54.
[5] Kekitiinwa Adeodata et al. 'Acceptability of Lopinavir/r Minitabs (Pellets), Tablets and Syrups in HIV-Infected Children' (2015, Feb) Poster presented at CROI, Seattle Washington. http://www.croiconference.org/sessions/acceptability-lopinavirr-minitabs-tablets-and-syrups-hiv-infected-children
[6] 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. See dosing table above.
[7] Dosing for children ≥ 35kg may follow adult recommendations using LPV/r 200mg/50mg tablets.

HOW TO ADMINISTER LPV/r ORAL PELLETS

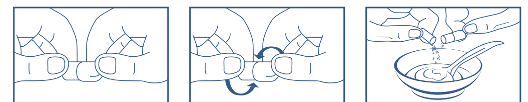
Important Note

The capsules containing LPV/r oral pellets **MUST NOT** be swallowed whole.

For infants and young children **older than 6 months** of age who are able to take soft foods:

- Open the bottle, count and remove the exact number of capsules required for the immediate dose as prescribed. Place these on a clean surface and close the bottle.
- Hold the capsule on both ends and, twisting in opposite direction and pull apart to deliver pellets **over** a small amount of soft food such as porridge at room temperature.

Adapted from Cipla package insert approved by USFDA



- The pellets **MUST NOT** be stirred, crushed, dissolved/dispersed in food, or chewed.
- Administer the entire dose of pellets with food to the child immediately.
- It is important to make sure the child has taken the entire dose of pellets by limiting the food used to an amount the child is able to easily consume in one swallow (e.g. 1 teaspoon), which may be followed by additional food to ensure the full dose is ingested.
- No mixture of the pellets and food is to be stored for later use.
- Dispose of the capsule shell in routine waste.

For infants not yet taking solid food, i.e. less than 6 months of age:

There is currently no experience administering pellets to infants < 3 months.[8] In the youngest infants of the CHAPAS 2 study (3-6 months of age), oral pellets[9] were added to a small volume of expressed breastmilk in a spoon and given to the infant or put directly on the infant's tongue before breastfeeding. Since **oral pellets CANNOT be stirred, dissolved/dispersed or crushed in liquids** prior to administration it is important to ensure that infants are developmentally able to swallow them.

- Open the bottle, count and remove the exact number of capsules required for the immediate dose as prescribed. Place these on a clean surface and close the bottle.
- Hold the capsule on both ends and, twisting in opposite direction pull capsule apart. Pellets can be added to a small volume of expressed breast milk or formula in a spoon and given to the infant or put directly on the infant's tongue before breastfeeding.
- Administer the entire dose of pellets to the infant immediately.
- It is important to make sure the infant has taken the entire dose of pellets by limiting the breastmilk (or formula) used to an amount the infant is able to easily consume in few swallows (e.g. two or three teaspoons), which may be followed by additional breastmilk (or formula) to ensure the full dose is ingested.
- Dispose of the capsule shells in routine waste.

[8] Further information about the safety of LPV/r pellets in young infants and implementation guidance on administration of pellets is anticipated from the LIVING study: https://clinicaltrials.gov/ct2/show/NCT02346487

[9] Referred to as minitabs in the CHAPAS 2 Trial

INFORMATION FOR HEALTHCARE PROVIDERS

- Adequate instructions must be provided to the caregiver or older child regarding administration of the oral pellets to ensure the correct number of capsules is opened and the entire dose is administered as required.
- It may be useful to **DEMONSTRATE** how to administer the **FIRST** dose to the caregiver.
- If giving LPV/r pellets to infants < 6months it may also be helpful to **OBSERVE** administration of the first dose to ensure the infant swallows the full dose. Infants should be carefully observed for signs of aspiration which may include, coughing, choking, gagging or eye reddening.
- The reason why the pellets should not be broken, crushed, chewed, or allowed to dissolve is to maintain the integrity of this dosage form, which is melt-extrusion matrix similar to LPV/r 100mg/25mg heat-stable tablets, which, when crushed or broken may significantly decrease drug exposure.[10]
- The recommended soft food should be one that does not require chewing to minimize the chances of the child chewing or crushing the pellets.
- Consider using LPV/r oral liquid, as per the table below, for infants who are unable to swallow solid particles such as the pellets.
- Consider using LPV/r 100mg/25mg tablets, as per the table below, for older children who can swallow tablets to avoid the need to open and administer a high number of LPV/r pellet capsules.

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[11]	2	2	1 ml	1 ml	NR	NR
5-5.9 kg	2	2	1 ml	1 ml	NR	NR
6 - 9.9kg	3	3	1.5 ml	1.5 ml	NR	NR
10- 13.9kg	4	4	2 ml	2 ml	2	1
14 - 19.9kg	5	5	2.5 ml	2.5 ml	2	2
20 - 24.9kg	6	6	3 ml	3 ml	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 dosages of recommended antiretroviral drugs

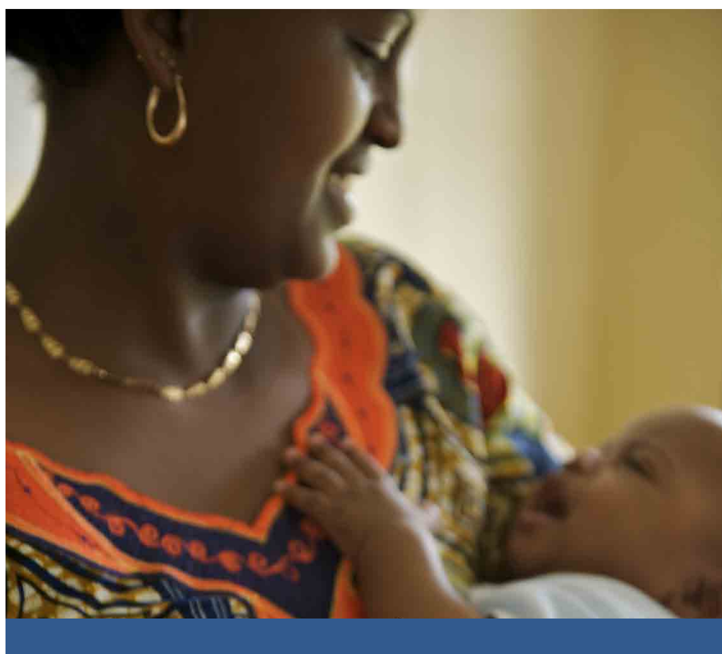
[10] Best, B et al "Pharmacokinetics of Lopinavir/Ritonavir Crushed versus Whole Tablets in Children" *J Acquir Immune Defic Syndr*, 2011 Dec 1, 58(4): 385-391.
[11] The USFDA has approved the use of pellets in children ≥ 5kg, though the safety of dosing infants 3-4.9 kg has been demonstrated in a small number of infants in CHAPAS-2.
The pellets may be administered in this weight band if infants are developmentally able to swallow them.

SUPPLY AND RECOMMENDED STORAGE AND HANDLING OF LPV/r oral pellets

Lopinavir/Ritonavir oral pellets 40mg/10mg per capsules are supplied in bottles containing 120 capsules. It should:

1 - Be transported and stored in the original container.
2 - Be transported and stored at temperatures **NOT EXCEEDING** 30°C (86°F).
3 - Not be exposed to high humidity outside the original container for longer than two weeks.

NOTE: Further guidance for procurement and supply chain management will be forthcoming from the IATT on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children (IATT) and the Paediatric ARV Procurement Working Group (PAPWG).



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Disclaimer:

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