



# World Health Organization

## NOTE TO NATIONAL AIDS PROGRAMMES, PROCUREMENT AGENTS AND STAKEHOLDERS ON THE POTENTIAL STOCK-OUT OF PAEDIATRIC DDI 25MG AND 50MG BUFFERED TABLETS

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### Background

Recent developments in the manufacture of buffered chewable didanosine (ddl) tablets for children may lead to a global shortage of ddl 25mg and 50mg tablets in the last quarter of 2010 and during the first quarter of 2011. This note seeks to provide guidance to national AIDS programmes, procurement agencies and partner organizations on how to mitigate the clinical impact of any potential stock-out.

Didanosine (ddl) is one of the oldest antiretroviral medicines (ARVs) in paediatric practice. It was licensed for use in children in 1991 and was the second drug ever approved for the treatment of HIV. It is a nucleoside reverse transcriptase inhibitor (NRTI) that has a resistance profile distinct from zidovudine (AZT) and stavudine (d4T). In the World Health Organization (WHO) 2010 paediatric antiretroviral therapy guidelines<sup>1</sup>, ddl is recommended as an *alternative* option for second-line treatment. However, ddl remains an important drug in clinical practice and was used by an estimated 5 000 children in low- and middle-income countries at the end of 2009<sup>2</sup>.

Three formulations of ddl are available for use in children:

1. Ddl powder for reconstitution (available in 2g and 4g pack sizes reconstituted to a final concentration of 10mg/ml)

The powder must be reconstituted with equal parts of water and a liquid antacid preparation, and the resulting suspension needs to be refrigerated. These constraints make it difficult to use ddl powder in resource-limited settings, but ddl suspension may be useful in some regions where the local health infrastructure makes it feasible to prepare and dispense this formulation.

2. Ddl buffered or “chewable” tablets (available as 25, 50, 100, 150 and 200 mg tablets)

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<sup>1</sup> Antiretroviral therapy for HIV infection in infants and children: Towards universal access. Executive summary of recommendations. Preliminary version for program planning. World Health Organization, Geneva, 2010.  
[http://www.who.int/hiv/pub/paediatric/paed\\_prelim\\_summary/en/index.html](http://www.who.int/hiv/pub/paediatric/paed_prelim_summary/en/index.html)

<sup>2</sup> Source: Survey on ARV use in low and middle-income countries, World Health Organization, 2010.

Buffered tablets must be chewed in the mouth or crushed before being swallowed in order to release the buffering antacid that is contained inside the tablets. In addition, buffered tablets should be dosed twice daily and in order to achieve optimal buffering, two buffered tablets should be consumed with every dose.

3. Ddl enteric-coated (EC) capsules (available as 125mg, 200mg, 250mg and 400mg capsules)

EC capsules are now the most commonly used formulations of ddl and have largely replaced buffered tablets for adults. These capsules contain small “beadlets” of ddl, each of which is enteric-coated, to prevent gastric acid from degrading the drug while it is in the stomach. Unlike the buffered tablets which have a minimum pill burden of 2 tablets per dose taken twice daily, EC capsules are dosed as one capsule once daily. EC capsules are also better tolerated than buffered tablets with fewer gastro-intestinal side-effects such as diarrhoea.

### **Dosing guidance**

WHO provides guidance on how to dose all three formulations in children (Annex A).

- For children between 5 and 10kg, the enteric-coated formulations cannot be used and the liquid or buffered tablets are the only acceptable options. However, because the liquid is difficult to reconstitute and store, the buffered tablets are preferred. In WHO's new paediatric guidelines, dosing recommendations are provided for only the 25mg buffered tablets. Tablets of higher strength, such as the 50mg tablet, can be used in children; however, because of the requirement that a minimum of 2 tablets be administered per dose, the 25mg tablets are the preferred option.
- For children weighing between than 6 and 10kg, the given dose is three 25mg buffered tablets in the morning and the two 25mg tablets in the evening. Two of the three 25mg tablets that make up the morning dose may be replaced by one tablet of 50mg.
- For children above 10kg, EC capsules are preferred. EC capsules should be swallowed whole. For children who cannot swallow the capsules, WHO recommends that the capsules be opened, and the beadlets sprinkled onto a small amount of food (not a meal) and ingested immediately. Ddl 100mg buffered tablets are sometimes used in older children, but are not recommended by WHO as the enteric-coated formulations are readily available, easier to take, and better tolerated.

### **Supply constraints with 25mg and 50mg buffered tablets**

In December 2009, Bristol Myers Squibb informed funding and procurement agencies that they would be able to provide only a limited supply of 25 and 50mg buffered ddl tablets between April 2010 and February 2011, as they move ddl production from one manufacturing plant to another. Bristol Myers Squibb is the only WHO pre-qualified supplier of these two products raising concerns that the interruption in supply could cause a worldwide shortage that might impact the clinical care of children receiving ddl.

WHO and other international partners are engaged in discussions with suppliers to address the potential stock-outs of ddl and identify solutions to secure the future availability of child-friendly ddl formulations. Meanwhile, for national programmes, WHO recommends a series of short-term actions, listed below, to better gauge the likelihood of a stock-out and minimize the impact of any potential shortfall. In addition, a number of longer-term actions are also recommended with the aim of rationalizing the use of ddl products in children in line with the new WHO normative guidance on the use of ARVs in second-line therapy.

### **Short-term Recommendations for National AIDS Programmes:**

1. Map out stocks of ddl 25mg and 50mg tablets at all drug-storage facilities and procurement agencies in order to determine current national inventory.
2. Assess the numbers of children under 10kg on treatment with ddl and estimate the need for 25mg and 50mg buffered tablets of ddl over a 12-month period, in accordance with the dosing guidance provided in Annex A.
3. Compare need with stock availability taking into consideration that 50mg tablets may be used to deliver part of the morning dose in children between 6 and 9.9 kg.
4. If stock is **not** sufficient to meet demand, put the following measures in place to minimize the consequences of stock-out:
  - a. Issue a memo to all providers that prescribe and pharmacies that dispense paediatric second-line ART to re-iterate dosing instructions on the use of ddl in children. Elements of the memo should include the appropriate use of buffered tablets of ddl (must be dosed twice daily and with two tablets in each dose) and the clinical superiority of EC capsules for children over 10kg. Buffered tablets should NOT be used in patients who can be dosed with EC formulations. A separate pull-out dosing table that shows the preferred formulations for each weight bracket (Annex B), could be helpful to reinforce proper use of ddl and the optimal selection of formulations and dose.
  - b. EC capsules should be available at all sites for older children to preserve stocks of 25mg and 50mg buffered tablets.
  - c. Anticipate any stock-out by adopting one or more of the following strategies:
    - i. Procure ddl liquid as a short-term measure to substitute for the 25mg and 50mg buffered tablets,
    - ii. Use 3TC instead of ddl in line with the new WHO guidelines which recommend ddl as an alternative (but not primary) option for second-line treatment,
    - iii. Consider the short-term use of 125mg EC capsules given once a day in children below 10kg and above 6kg. Note that although the total daily dose in this group is 125mg of ddl, once-daily dosing of ddl has not been tested in children in this weight range.

### **Long-term Recommendations for National AIDS Programmes:**

1. Update the national formulary to ensure that paediatric formulations of ddl EC (125mg, and 200mg strengths) are readily available in countries from one of the several WHO pre-qualified or SRA approved suppliers. Aurobindo and Matrix have received tentative approval from the FDA for the 125mg and 200mg EC formulations. Multiple stringent regulatory authority (SRA)-approved sources are also available for the adult 250mg and 400mg EC formulations.
2. Revise national paediatric ART guidelines to align them with current WHO 2010 ART recommendations including:
  - a. Adopting dosing recommendations for use of different ddl formulations as stipulated within Annex A of the new paediatric guidelines,
  - b. Revising second-line treatment recommendations for children to use the new preferred options for second-line which include ABC and 3TC or AZT and 3TC but not ddl.

Annex A - WHO Dosing guidance for dDI formulations available for use in children

**Didanosine****Recommended dosing based on weight-bands for children >3 months using liquid and chewable tablets**

Weight range (kg)		Target dose 3 months to <13 years: 90–120 mg/m <sup>2</sup> /dose twice daily		Dose (ml or tablets)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	10	mg/ml liquid	NR	NR
4	4.9	10	mg/ml liquid	NR	NR
5	5.9	10	mg/ml liquid	3 ml	3 ml
6	6.9	10	mg/ml liquid	5 ml	5 ml
7	7.9	10	mg/ml liquid	5 ml	5 ml
8	8.9	10	mg/ml liquid	5 ml	5 ml
9	9.9	10	mg/ml liquid	5 ml	5 ml
10	10.9	10	mg/ml liquid	6 ml	6 ml
11	11.9	10	mg/ml liquid	6 ml	6 ml
12	13.9	10	mg/ml liquid	6 ml	6 ml
14	16.9	25	mg tablet	4	3
17	19.9	25	mg tablet	4	3
20	24.9	25	mg tablet	4	4
25	29.9	25	mg tablet	5	5
30	34.9	25	mg tablet	5	5

Note: 25mg chewable tablets can be substituted with other strengths to the same mg amount but each a.m. and p.m. dose must always be made up of at least two tablets.

NR not recommended

**Didanosine**  
**Recommended dosing based on weight-bands for children >3 months using chewable tablets**

Weight range (kg)		Target dose 3 months to <13 years: 90–120 mg/m <sup>2</sup> /dose twice daily		Dose (tablet)	
Bottom	Top	Formulation		a.m.	p.m.
3	3.9	25	mg tablet	NR	NR
4	4.9	25	mg tablet	NR	NR
5	5.9	25	mg tablet	2	2
6	6.9	25	mg tablet	3	2
7	7.9	25	mg tablet	3	2
8	8.9	25	mg tablet	3	2
9	9.9	25	mg tablet	3	2
10	10.9	25	mg tablet	3	3
11	11.9	25	mg tablet	3	3
12	13.9	25	mg tablet	3	3
14	16.9	25	mg tablet	4	3
17	19.9	25	mg tablet	4	3
20	24.9	25	mg tablet	4	4
25	29.9	25	mg tablet	5	5
30	34.9	25	mg tablet	5	5

Note: 25mg chewable tablets can be substituted with other strengths to the same mg amount but each a.m. and p.m. dose must always be made up of at least two tablets.  
 NR not recommended

**Didanosine**  
**Recommended once-daily dosing based on weight-bands using enteric-coated capsules**

Weight range (kg)		Target dose 240–300 mg/m <sup>2</sup> /day		Dose (ml or tablets)
Bottom	Top	Formulation		a.m. or p.m.
3	3.9	NR		NR
4	4.9	NR		NR
5	5.9	NR		NR
6	6.9	NR		NR
7	7.9	NR		NR
8	8.9	NR		NR
9	9.9	NR		NR
10	10.9	125	mg EC capsule	1
11	11.9	125	mg EC capsule	1
12	13.9	125	mg EC capsule	1
14	16.9	200	mg EC capsule	1
17	19.9	200	mg EC capsule	1
20	24.9	125	mg EC capsule	2
25	29.9	125	mg EC capsule	2
30	34.9	125	mg EC capsule	2

NR not recommended

Annex B - WHO Dosing guidance for dDI formulations available for use in children with the preferred formulations in different weight brackets

Weight band (kg)			Formulation	Dosing
5	To	5.9	25mg buffered tab	2 x 25mg tab twice a day
6	To	6.9	25mg buffered tab	3 x 25mg tab am/2 x 25mg tab pm
7	To	7.9	25mg buffered tab	3 x 25mg tab am/2 x 25mg tab pm
8	To	8.9	25mg buffered tab	3 x 25mg tab am/2 x 25mg tab pm
9	To	9.9	25mg buffered tab	3 x 25mg tab am/2 x 25mg tab pm
10	To	10.9	125mg EC capsule	1 x 125mg cap once a day
11	To	11.9	125mg EC capsule	1 x 125mg cap once a day
12	To	13.9	125mg EC capsule	1 x 125mg cap once a day
14	To	16.9	200mg EC capsule	1 x 200mg cap once a day
17	To	19.9	200mg EC capsule	1 x 200mg cap once a day
20	To	24.9	250mg EC capsule	1 x 250mg cap once a day
25	To	29.9	250mg EC capsule	1 x 250mg cap once a day
30	To	34.9	250mg EC capsule	1 x 250mg cap once a day