

## Dosing instructions for the use of currently available fixed-dose combination TB medicines for children

### Introduction

The initiative for better medicines for children has led to the examination of appropriate dose recommendations for anti tuberculosis medicines, specific to the needs of children.

A systematic review of evidence for appropriate doses of first line medicines for TB has been completed. Based on this review and consultations<sup>1,2</sup>, the WHO recommendations for these medicines have been revised to be as follows, according to weight:

- rifampicin: 15 mg/kg/d (10 to 20 mg/kg/day)
- isoniazid: 10 mg/kg/d (10 to 15 mg/kg/day)
- pyrazinamide: 35 mg/kg/d (30 to 40 mg/kg/day).

Ethambutol has previously been recommended at a dose of 20 mg/kg/d (15 mg to 25 mg/kg/d).

It has now been proposed by the Expert Committee on Selection and Use of Essential Medicines<sup>3</sup> that a **Fixed Dose Combination (FDC) containing rifampicin 250 mg, isoniazid 150 mg, pyrazinamide 400 mg, and ethambutol 250 mg**, would be the ideal product for the treatment regimen for the intensive phase of treatment in children between 5 kg and 30 kg, especially if the product is formulated as a flexible oral solid dosage form, such as a dispersible tablet. These specifications are based on ranges of doses of each medicine that would be predicted to achieve optimum serum levels at steady state.

Other combinations that would also be useful would be a **3-component product containing rifampicin 250 mg + isoniazid 150 mg + pyrazinamide 400 mg**, for situations where ethambutol is not included in the intensive phase, and a **2 component product, rifampicin 250 mg + isoniazid 150 mg**, for the continuation phase of treatment.

**However, no quality assured versions of products meeting these specifications are currently known to exist.**

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1 [http://www.who.int/selection\\_medicines/committees/expert/17/application/TB/en/index.html](http://www.who.int/selection_medicines/committees/expert/17/application/TB/en/index.html)

2 [http://www.who.int/selection\\_medicines/committees/subcommittee/2/TB.pdf](http://www.who.int/selection_medicines/committees/subcommittee/2/TB.pdf)

3 [http://www.who.int/selection\\_medicines/committees/expert/17/WEBuneditedTRS\\_2009.pdf](http://www.who.int/selection_medicines/committees/expert/17/WEBuneditedTRS_2009.pdf)

Currently, FDCs of the following strengths have been approved by the WHO-UN prequalification program:

- rifampicin+ isoniazid: 60mg +30mg dispersible
- rifampicin+ isoniazid+ pyrazinamide: 60mg+30mg+150mg dispersible
- rifampicin +isoniazid: 150mg+75mg tablet
- rifampicin+ isoniazid+ ethambutol: 150mg+75mg+275mg tablet.
- rifampicin+ isoniazid+ pyrazinamide+ ethambutol: 150mg+75mg+400mg+275mg tablet.

Two other FDCs that are available under GDF Quality Assurance policy are:

- rifampicin+ isoniazid: 60mg+60mg dispersible
- rifampicin +isoniazid: 150mg+150mg tablet

NONE OF THESE ALONE ARE IDEAL FOR CHILDREN.

**As an interim measure**, to utilize the currently available products appropriately to achieve the desirable doses of medicines for children, the following dosing charts have been constructed, based on the assumptions listed below:

- Quality assured dispersible tablets should be used wherever possible, especially for children who cannot swallow solid tablets.
- Regimens are based on FDCs, but in some case may also require administration of single component products
- These doses are for **once a day** dosing regimens and wherever possible, do NOT require splitting tablets.
- The recommended doses are generally below the upper limit of the dose ranges specified above, to minimize risk of toxicity.

The tables list administered dose, and likely achieved dose (mg/kg). Simplified versions have been prepared for circulation to program workers, see Document 2.

ALL children being treated for TB should be weighed at least once every month to allow for adjustment of dosage administered as necessary.

**Table 1.A. is for the intensive phase of treatment without ethambutol, that can be used for children from 5kg up to the weight of 20 kg, using the following products:**

- rifampicin+ isoniazid: 60+60 dispersible.
- rifampicin+ isoniazid+ pyrazinamide: 60+30+150 dispersible.

**Table 1.B. is for the intensive phase of treatment including ethambutol, that can be used for children from 5kg up to the weight of 20kg, using the following products:**

- rifampicin+ isoniazid: 60+60 dispersible.
- rifampicin+ isoniazid+ pyrazinamide: 60+30+150 dispersible.
- ethambutol tablet (100mg)

*Note that this regimen requires a tablet that is not dispersible and is therefore recommended for use only in children who can swallow solid tablets.*

**Table 2.A. is for the continuation phase of treatment of new cases in children from 5 kg-20 kg, using the following products:**

- rifampicin+ isoniazid: 60+60 dispersible
- rifampicin+ isoniazid: 60+30 dispersible.

*This combination in particular requires care to avoid confusion between the two products, to avoid under-dosing or toxicity for isoniazid.*

**Table 2.B. is for the continuation phase of cases undergoing retreatment in children from 5kg-20kg, using the following products:**

- rifampicin+ isoniazid: 60+60 dispersible
- rifampicin+ isoniazid: 60+30 dispersible.
- ethambutol tablet (100mg)

*Note that this regimen requires a tablet that is not dispersible and is therefore recommended for use only in children who can swallow solid tablets.*

*This combination in particular requires care to avoid confusion between the two FDC products, to avoid under-dosing or toxicity for isoniazid.*

**Table 3.A. is the intensive phase of treatment without ethambutol, that can be used for children from 21kg up to the weight of 30 kg, using the following products:**

- rifampicin+ isoniazid: 60+60 dispersible
- rifampicin+ isoniazid 150+75 tablet
- pyrazinamide tablet (400mg)

*Note that this regimen requires 2 tablets that are not dispersible and is therefore recommended for use only in children who can swallow solid tablets.*

**Table 3.B. is for the intensive phase of treatment including ethambutol, that can be used for children from 21 kg- 30kg, using the following products:**

- rifampicin+ isoniazid: 60+60 dispersible.
- rifampicin+ isoniazid+ pyrazinamide+ ethambutol: 150+75+400+275 tablet

*Note that this regimen requires a tablet that is not dispersible and is therefore recommended for use only in children who can swallow solid tablets.*

**Table 4.A. is for the continuation phase of treatment of *new cases* in children from 21 kg-30 kg, using the following products:**

- rifampicin+ isoniazid: 60+60 dispersible.
- rifampicin+ isoniazid: 150+75 tablet

*Note that this regimen requires a tablet that is not dispersible and is therefore recommended for use only in children who can swallow solid tablets.*

**Table 4.B. is for the continuation phase of cases undergoing retreatment in children from 21kg-30kg, using the following products:**

- rifampicin+ isoniazid: 60+60 dispersible.
- rifampicin+ isoniazid: 150+75 tablet
- ethambutol tablet (400mg)

*Note that this regimen requires 2 tablets that are not dispersible and is therefore recommended for use only in children who can swallow solid tablets.*

Children weighing more than 30 kg should be treated according to the current adult treatment guidelines.

Table Keys:

<sup>∞</sup> Over target range: monitor for toxicity

<sup>r</sup> Under target range: consider increasing dose if clinically indicated

Weight band 1
Weight band 2
Weight band 3

**Table 1.A. : Interim recommendation for intensive phase using dispersible FDCs (rifampicin, isoniazid, pyrazinamide: 60+30+150 and rifampicin, isoniazid: 60+60)**

Weight (kg)	Rifampicin, isoniazid, pyrazinamide dispersible (60,30,150)	Rifampicin, isoniazid dispersible (60,60)	Rifampicin (mg/kg)	Isoniazid (mg/kg)	Pyrazinamide (mg/kg)
5	1	1	24.0 <sup>∞</sup>	18 <sup>∞</sup>	30.0
6	1	1	20.0	15.0	25.0 <sup>r</sup>
7	1	1	17.1	12.9	21.4 <sup>r</sup>
8	2	1	22.5 <sup>∞</sup>	15.0	37.5
9	2	1	20.0	13.3	33.3
10	2	1	18.0	12.0	30.0
11	2	1	16.4	10.9	27.3 <sup>r</sup>
12	2	1	15.0	10.0	25.0 <sup>r</sup>
13	2	1	13.8	9.2 <sup>r</sup>	23.1 <sup>r</sup>
14	2	1	12.9	8.6 <sup>r</sup>	21.4 <sup>r</sup>
15	3	2	20.0	14.0	30.0
16	3	2	18.8	13.1	28.1 <sup>r</sup>
17	3	2	17.6	12.4	26.5 <sup>r</sup>
18	3	2	16.7	11.7	25.0 <sup>r</sup>
19	3	2	15.8	11.1	23.7 <sup>r</sup>
20	3	2	15.0	10.5	22.5 <sup>r</sup>

**Table 1.B. : Interim recommendation for intensive phase using dispersible FDCs (rifampicin, isoniazid, pyrazinamide: 60+30+150 and rifampicin, isoniazid: 60+60) and ethambutol tablet (100mg)**

Weight (kg)	Rifampicin, isoniazid, pyrazinamide dispersible (60,30,150)	Rifampicin, isoniazid dispersible (60,60)	Ethambutol tablet (100)	Rifampicin (mg/kg)	Isoniazid (mg/kg)	Pyrazinamide (mg/kg)	Ethambutol (mg/kg)
5	1	1	1	24.0 <sup>∞</sup>	18 <sup>∞</sup>	30.0	20.0
6	1	1	1	20.0	15.0	25.0 <sup>Y</sup>	16.7
7	1	1	1	17.1	12.9	21.4 <sup>Y</sup>	14.3 <sup>Y</sup>
8	2	1	2	22.5 <sup>∞</sup>	15.0	37.5	25.0
9	2	1	2	20.0	13.3	33.3	22.2
10	2	1	2	18.0	12.0	30.0	20.0
11	2	1	2	16.4	10.9	27.3 <sup>Y</sup>	18.2
12	2	1	2	15.0	10.0	25.0 <sup>Y</sup>	16.7
13	2	1	2	13.8	9.2 <sup>Y</sup>	23.1 <sup>Y</sup>	15.4
14	2	1	2	12.9	8.6 <sup>Y</sup>	21.4 <sup>Y</sup>	14.3 <sup>Y</sup>
15	3	2	3	20.0	14.0	30.0	20.0
16	3	2	3	18.8	13.1	28.1 <sup>Y</sup>	18.8
17	3	2	3	17.6	12.4	26.5 <sup>Y</sup>	17.6
18	3	2	3	16.7	11.7	25.0 <sup>Y</sup>	16.7
19	3	2	3	15.8	11.1	23.7 <sup>Y</sup>	15.8
20	3	2	3	15.0	10.5	22.5 <sup>Y</sup>	15.0

**Table 2.A :** Interim recommendation for continuation phase in new cases using dispersible FDCs (rifampicin, isoniazid: 60+30 and rifampicin, isoniazid: 60+60)

Weight (kg)	Rifampicin, isoniazid <i>dispersible</i> (60,30)	Rifampicin, isoniazid <i>dispersible</i> (60,60)	Rifampicin (mg/kg)	Isoniazid (mg/kg)
5	1	1	24.0 <sup>∞</sup>	18.0 <sup>∞</sup>
6	1	1	20.0	15.0
7	1	1	17.1	12.9
8	2	1	22.5 <sup>∞</sup>	15.0
9	2	1	20.0	13.3
10	2	1	18.0	12.0
11	2	1	16.4	10.9
12	2	1	15.0	10.0
13	2	1	13.8	9.2 <sup>r</sup>
14	2	1	12.9	8.6 <sup>r</sup>
15	3	2	20.0	14.0
16	3	2	18.8	13.1
17	3	2	17.6	12.4
18	3	2	16.7	11.7
19	3	2	15.8	11.1
20	3	2	15.0	10.5

**Table 2.B. : Interim recommendation for continuation phase in retreatment cases using dispersible FDCs (rifampicin, isoniazid: 60+30 and rifampicin, isoniazid: 60+60) and ethambutol tablet (100mg)**

Weight (kg)	Rifampicin, isoniazid dispersible (60,30)	Rifampicin, isoniazid dispersible (60,60)	Ethambutol tablet (100)	Rifampicin (mg/kg)	Isoniazid (mg/kg)	Ethambutol (mg/kg)
5	1	1	1	24.0 <sup>∞</sup>	18 <sup>∞</sup>	20.0
6	1	1	1	20.0	15.0	16.7
7	1	1	1	17.1	12.9	14.3 <sup>r</sup>
8	2	1	2	22.5 <sup>∞</sup>	15.0	25.0
9	2	1	2	20.0	13.3	22.2
10	2	1	2	18.0	12.0	20.0
11	2	1	2	16.4	10.9	18.2
12	2	1	2	15.0	10.0	16.7
13	2	1	2	13.8	9.2 <sup>r</sup>	15.4
14	2	1	2	12.9	8.6 <sup>r</sup>	14.3 <sup>r</sup>
15	3	2	3	20.0	14.0	20.0
16	3	2	3	18.8	13.1	18.8
17	3	2	3	17.6	12.4	17.6
18	3	2	3	16.7	11.7	16.7
19	3	2	3	15.8	11.1	15.8
20	3	2	3	15.0	10.5	15.0

**Table 3.A :** Interim recommendation for intensive phase using FDC tablet (rifampicin, isoniazid: 150+75), dispersible FDC (rifampicin, isoniazid: 60+60) and pyrazinamide tablet (400mg)

Weight (kg)	Rifampicin, isoniazid tablet (150,75)	Rifampicin, isoniazid dispersible (60,60)	Pyrazinamide tablet (400)	Rifampicin (mg/kg)	Isoniazid (mg/kg)	Pyrazinamide (mg/kg)
21	2	2	2	20.0	12.9	38.1
22	2	2	2	19.1	12.3	36.4
23	2	2	2	18.3	11.7	34.8
24	2	2	2	17.5	11.3	33.3
25	2	2	2	16.8	10.8	32.0
26	2	2	2	16.2	10.4	30.8
27	2	2	2	15.6	10.0	29.6 <sup>r</sup>
28	2	2	2	15.0	9.6 <sup>r</sup>	28.6 <sup>r</sup>
29	2	2	2	14.5	9.3 <sup>r</sup>	27.6 <sup>r</sup>
30	2	2	2	14.0	9.0 <sup>r</sup>	26.7 <sup>r</sup>

**Table 3.B :** Interim recommendation for intensive phase using 4FDC tablet (rifampicin, isoniazid, pyrazinamide, ethambutol: 150+75+400+275) and dispersible FDC (rifampicin, isoniazid: 60+60)

Weight (kg)	Rifampicin, isoniazid, pyrazinamide, ethambutol tablet (150,75,400,275)	Rifampicin, isoniazid dispersible (60,60)	Rifampicin (mg/kg)	Isoniazid (mg/kg)	Pyrazinamide (mg/kg)	Ethambutol (mg/kg)
21	2	2	20.0	12.9	38.1	26.2 <sup>∞</sup>
22	2	2	19.1	12.3	36.4	25.0
23	2	2	18.3	11.7	34.8	23.9
24	2	2	17.5	11.3	33.3	22.9
25	2	2	16.8	10.8	32.0	22.0
26	2	2	16.2	10.4	30.8	21.2
27	2	2	15.6	10.0	29.6 <sup>r</sup>	20.4
28	2	2	15.0	9.6 <sup>r</sup>	28.6 <sup>r</sup>	19.6
29	2	2	14.5	9.3 <sup>r</sup>	27.6 <sup>r</sup>	19.0
30	2	2	14.0	9.0 <sup>r</sup>	26.7 <sup>r</sup>	18.3

**Table 4.A. : Interim recommendation for continuation phase in new cases using FDC tablet (rifampicin, isoniazid: 150+75) and dispersible FDC (rifampicin, isoniazid: 60+60)**

Weight (kg)	Rifampicin, isoniazid <i>tablet</i> (150,75)	Rifampicin, isoniazid <i>dispersible</i> (60,60)	Rifampicin (mg/kg)	Isoniazid (mg/kg)
21	2	2	20.0	12.9
22	2	2	19.1	12.3
23	2	2	18.3	11.7
24	2	2	17.5	11.3
25	2	2	16.8	10.8
26	2	2	16.2	10.4
27	2	2	15.6	10.0
28	2	2	15.0	9.6 <sup>r</sup>
29	2	2	14.5	9.3 <sup>r</sup>
30	2	2	14.0	9.0 <sup>r</sup>

**Table 4.B. : Interim recommendation for continuation phase in retreatment cases using FDC tablet (rifampicin, isoniazid: 150+75), dispersible FDC (rifampicin, isoniazid: 60+60) and ethambutol tablet (400mg)**

Weight (kg)	Rifampicin, isoniazid <i>tablet</i> (150,75)	Rifampicin, isoniazid <i>dispersible</i> (60,60)	Ethambutol <i>tablet</i> (400)	Rifampicin (mg/kg)	Isoniazid (mg/kg)	Ethambutol (mg/kg)
21	2	2	1	20.0	12.9	19.0
22	2	2	1	19.1	12.3	18.2
23	2	2	1	18.3	11.7	17.4
24	2	2	1	17.5	11.3	16.7
25	2	2	1	16.8	10.8	16.0
26	2	2	1	16.2	10.4	15.4
27	2	2	1	15.6	10.0	14.8 <sup>r</sup>
28	2	2	1	15.0	9.6 <sup>r</sup>	14.3 <sup>r</sup>
29	2	2	1	14.5	9.3 <sup>r</sup>	13.8 <sup>r</sup>
30	2	2	1	14.0	9.0 <sup>r</sup>	13.3 <sup>r</sup>