

5. THE USE OF CO-TRIMOXAZOLE PROPHYLAXIS FOR HIV-RELATED INFECTIONS AMONG ADULTS, ADOLESCENTS AND CHILDREN

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 8 – Prevention, screening and management of common coinfections

5.1 Background

Co-trimoxazole is a fixed-dose combination of two antimicrobial drugs (sulfamethoxazole and trimethoprim) that covers a variety of bacterial, fungal and protozoan infections. Co-trimoxazole preventive therapy is a feasible, well tolerated and inexpensive intervention for people living with HIV to reduce HIV-related morbidity and mortality (1). Further, co-trimoxazole is an off-patent drug and widely available in resource-limited settings. In 2006, WHO guidelines on co-

trimoxazole prophylaxis in resource-limited settings (2) were issued. The guidelines recommend co-trimoxazole prophylaxis to be implemented as an integral component of the HIV care package. Importantly, these guidelines noted the effectiveness of co-trimoxazole prophylaxis in reducing mortality and morbidity across varying levels of background resistance to co-trimoxazole and the prevalence of malaria. The expanded access and progressive movement towards earlier initiation of ART warranted an update to existing WHO guidelines on co-trimoxazole prophylaxis.

5.2 Co-trimoxazole prophylaxis for adults

- Co-trimoxazole prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with a CD4 count of ≤ 350 cells/mm³.

(Strong recommendation, moderate-quality evidence)

- In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage.

(Conditional recommendation, moderate-quality evidence)

- Co-trimoxazole prophylaxis may be discontinued for adults (including pregnant women) with HIV infection who are clinically stable on ART, with evidence of immune recovery and viral suppression.

(Conditional recommendation, low-quality evidence)

- In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage.

(Conditional recommendation, moderate-quality evidence)

- Routine co-trimoxazole prophylaxis should be administered to all HIV-infected people with active TB disease regardless of CD4 cell counts.

(Strong recommendation, high-quality evidence)^a

^aRecommendation maintained from WHO policy on collaborative TB/HIV policy activities: guidelines for national programmes and other stakeholders (49).

5.2.1 Rationale and supporting evidence for the use of co-trimoxazole prophylaxis for adults

5.2.1.1 When to start co-trimoxazole prophylaxis

Moderate-quality evidence from nine observational studies (3–11) supports the effectiveness of co-trimoxazole prophylaxis in reducing mortality risk among people starting ART with a CD4 cell count ≤ 350 cells/mm³. Overall, the GRADE assessment suggested limited risk of bias, imprecision and indirectness

in this body of observational literature. One study (11) also reviewed other outcomes and found a reduction in WHO stage 3 or 4 events (low-quality evidence) and malaria (low-quality evidence) and a low rate of treatment-limiting adverse events (low-quality evidence). Another study (7) found comparable rates of *Pneumocystis jirovecii* pneumonia (very-low-quality evidence).

A second GRADE assessment examined four studies of adults not on ART and with CD4 cell counts >350 cells/mm³

(12–15). In one randomized controlled trial (12), co-trimoxazole prophylaxis was shown to reduce the rates of new WHO stage 3 or 4 clinical events (high-quality evidence), severe bacterial infections (high-quality evidence), malaria (high-quality evidence) and hospitalization (high-quality evidence). Rates of TB, death and bacterial pneumonia were also reduced, but these effect estimates did not reach statistical significance (moderate-quality evidence). Finally, the rate of treatment-limiting adverse events was also low in this trial (high-quality evidence). Three observational studies reported a reduction in malaria (moderate-quality evidence).

The Guideline Development Group reasoned that the clinical benefits outweighed the additional pill burden and possible cost associated with co-trimoxazole prophylaxis. The Guideline Development Group also judged that co-trimoxazole prophylaxis was acceptable to health-care workers and the community living with HIV. The Guideline Development Group acknowledged operational feasibility and determined that there were no major barriers to uptake of this new WHO recommendation on initiating co-trimoxazole prophylaxis. Considering all these domains, the Guideline Development Group agreed on the initiation recommendations in adults.

5.2.1.2 When to stop co-trimoxazole prophylaxis

The risks and benefits of continuing versus stopping co-trimoxazole prophylaxis after immune recovery above 350 CD4 cells/mm³ were assessed. Two randomized trials (16,17) found that continuing co-trimoxazole reduced hospitalization, malaria, pneumonia and diarrhoea in settings where malaria and/or serious bacterial infections were highly prevalent (high-quality evidence). The rates of mortality and new stage 3 or 4 events were comparable in the study arms (moderate and low-quality evidence, respectively).

The risks and benefits of continuing versus stopping co-trimoxazole prophylaxis after viral suppression induced by ART were also evaluated in settings with a low burden of malaria and serious bacterial infections. Two studies (18,19) found that the rates of *Pneumocystis jirovecii* pneumonia and death were similar among people receiving ART who achieved viral suppression and had CD4 cell counts above 100 cells/mm³ in study arms. Guidelines are available from high-income countries to inform practice in these settings (20,21).

The Guideline Development Group determined that maintaining co-trimoxazole prophylaxis confers clinical benefits that outweigh the potential risks. The recommendation for settings with a high prevalence of malaria and/or severe bacterial infections may simplify HIV management, forecasting and supply management issues and improve co-trimoxazole prophylaxis access to people living with HIV. The Guideline Development Group also recognized that HIV-uninfected people may have a potential disadvantage in terms of diarrhoea, pneumonia

and malaria prevention over people who are infected with HIV and receiving co-trimoxazole. Given all these factors, the Guideline Development Group agreed on the discontinuation recommendations for adults using some clinical, immunological and virological parameters indicating immune recovery resulting from ART. However, in settings with a low prevalence of malaria and/or severe bacterial infections and limited or no access to CD4 testing, co-trimoxazole prophylaxis should not be discontinued.

5.2.2 Co-trimoxazole prophylaxis in pregnancy

In the 2006 guidelines, WHO (2) recommended that co-trimoxazole prophylaxis be initiated and maintained regardless of the stage of pregnancy in eligible women living with HIV. There have been concerns that folate depletion resulting from the use of co-trimoxazole (as well as sulfadoxine and pyrimethamine, which are commonly used for malaria prophylaxis) during pregnancy may result in an increased risk of teratogenicity (22,23). A systematic review identified 24 studies that evaluate co-trimoxazole use among women irrespective of HIV status, trimester of pregnancy, or purpose of use. The findings of this review support continued recommendations for co-trimoxazole as a priority intervention for HIV-infected pregnant women (24). Given the low quality of this evidence, the heterogeneity of results in studies and possible confounding (the reporting of folate supplementation is inconsistent), the Guideline Development Group could not conclude that co-trimoxazole exposure increases the risk of teratogenicity and that the benefits outweighed any potential risk. The Guideline Development Group endorsed the need to promote pregnancy registries and toxicity monitoring.

WHO recommends the intermittent preventive treatment of malaria in pregnancy¹ in settings with moderate-to-high malaria transmission (where malaria prevalence exceeds 10% among children 2–9 years old) (25). A systematic review identified two randomized trials (26,27), which found co-trimoxazole prophylaxis to be non-inferior to intermittent preventive treatment of malaria in pregnancy with respect to infant mortality, low birth weight (<2.5 kg), placental malaria, maternal death and treatment-limiting adverse events (high-quality evidence). Non-inferiority for clinical malaria could not be concluded (low-quality evidence). Based on these data, the Guideline Development Group determined that co-trimoxazole prophylaxis for pregnant women with HIV can be used to prevent malaria among infants and that pregnant women with HIV should follow the same principles as adults with HIV. Intermittent preventive treatment of malaria in pregnancy should not be provided in addition to co-trimoxazole prophylaxis.²

5.2.3 Dosing adults

The recommended dose of co-trimoxazole for adults living with HIV is 960 mg daily (800 mg sulfamethoxazole + 160

1. Intermittent preventive treatment of malaria in pregnancy provides antimalarial drugs to pregnant women at each scheduled antenatal care visit to reduce the complications of malaria in the infant and the mother.

2. Co-trimoxazole prophylaxis is dosed daily not intermittently.

mg trimethoprim, either as a 960-mg double-strength tablet or two 480-mg single-strength tablets). A systematic review examined whether a lower dose of co-trimoxazole (480 mg daily) could provide the same efficacy as 960 mg in preventing a broad spectrum of HIV-related infections. Two trials (28,29) found 480 mg to be non-inferior to 960 mg with respect to

death, *Pneumocystis jirovecii* pneumonia, toxoplasmosis, malaria, pneumonia and diarrhoea. However, there was no consistent reduction in treatment-limiting adverse events. The Guideline Development Group recommended maintaining 960 mg daily and recognized that further clinical and toxicity data are needed to propose a reduction in co-trimoxazole dose.

5.3 Co-trimoxazole prophylaxis for HIV-infected infants, children and adolescents³

- Co-trimoxazole prophylaxis is recommended for infants, children and adolescents with HIV, irrespective of clinical and immune conditions. Priority should be given to all children younger than 5 years old regardless of CD4 cell count or clinical stage and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with a CD4 count of ≤ 350 cells/mm³.

(Strong recommendation, high-quality evidence)

- In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued until adulthood irrespective of whether ART is provided.

(Conditional recommendation, moderate - quality evidence)

- In settings with low prevalence for both malaria and bacterial infections, co-trimoxazole prophylaxis may be discontinued for children 5 years of age and older who are clinically stable and/or virally suppressed on ART for at least 6 months and with a CD4 count >350 cells/mm³.

(Strong recommendation, very-low-quality evidence)

5.3.1 When to start co-trimoxazole prophylaxis

The existing evidence analysed through GRADE assessment supports the expansion of the initiation of co-trimoxazole prophylaxis to children with CD4 cell counts above the current threshold. These new recommendations were informed by the CHAP trial in Zambia, a double-blind, placebo-controlled randomized trial (30–33), which was interrupted because of sustained benefit in the co-trimoxazole prophylaxis group. This study found a 43% reduction in mortality irrespective of age and CD4 cell count at randomization (follow-up of median 1.9 years) ($P = 0.0002$) and co-trimoxazole prophylaxis was also associated with reduced rates of hospitalization (34). Of note, hospitalization associated with severe bacterial infections was the most common, even though there were overall few events for malaria and severe bacterial infections (35). Grade 3 or 4 adverse events were limited, with no significant difference across arms (30).

The CHAP trial has demonstrated overall that providing co-trimoxazole prophylaxis to children has survival benefit irrespective of age and CD4 cell count in settings where severe bacterial infections and/or malaria are highly prevalent. However, the Guideline Development Group acknowledged that most children in the CHAP trial, being immunocompromised, already met the criteria for initiating co-trimoxazole prophylaxis and recognized the uncertainty around the generalizability of these findings to children whose CD4 cell counts are higher by downgrading the quality of the evidence for indirectness and imprecision.

The Guideline Development Group considered the value of giving priority to children with advanced disease and immunosuppression to better reflect the quality of the evidence and to harmonize with adult recommendations, which was also considered important. Although there may be potential issues with the acceptability of the intervention, the individual and programmatic benefits of these revised recommendations appeared to outweigh the risks. In addition, providing co-trimoxazole prophylaxis to all children and adolescents was considered to be feasible given the low price of co-trimoxazole prophylaxis and the limited additional infrastructure needed to deliver co-trimoxazole prophylaxis (32). Overall, the strength of the recommendation was ranked as strong.

5.3.2 When to stop co-trimoxazole prophylaxis

The ARROW trial, a randomized, open-label non-inferiority trial undertaken in Uganda and Zimbabwe in 758 children 3 years and older who were receiving ART for at least 96 weeks (36), informed the recommendation on discontinuation made by the Guideline Development Group. Over a median of 2.1 years of follow-up of children and adolescents receiving ART, with median a CD4 cell count of 720 cells/mm³ (among those older than 5 years) and CD4 percentage of 33%, continuing co-trimoxazole prophylaxis was associated with fewer "deaths or hospitalization", and this effect was sustained over time and was observed in settings with and without malaria. Continuing co-trimoxazole prophylaxis was safe over the same follow-

3. WHO 2006 guidelines (2) recommended daily co-trimoxazole prophylaxis for HIV-infected children <2 years old and for those >2 years old with symptomatic disease or CD4 cell counts below age-related thresholds, but state that children >5 years old with good adherence after >6 months on ART, full clinical recovery and CD4 >350 cells/mm³ may discontinue.

up period, and no severe drug-related adverse events were observed (36).

The systematic review supports continuing co-trimoxazole prophylaxis throughout childhood, based on randomized trial data, which were considered to provide moderate-quality evidence. However, because long-term data on the benefits and potential toxicity are lacking, some uncertainty was observed around acceptability and the balance between risks and benefits. The feasibility and the cost implications of extending co-trimoxazole prophylaxis throughout childhood was not of concern, since the ARROW trial showed that continuing co-trimoxazole prophylaxis improved health outcomes at reduced costs (by reducing hospitalization). Overall, the strength of the recommendation was ranked as conditional.

In settings with a low prevalence of both malaria and severe bacterial infections and where the use of co-trimoxazole prophylaxis has the main goal of preventing *Pneumocystis jirovecii* pneumonia, the Guideline Development Group

agreed that discontinuation could be considered. It was supported by the evidence from two observational studies (37,38)⁴ conducted in Europe and the United States of America suggesting that co-trimoxazole prophylaxis could be safely discontinued in children and adolescents living with HIV with a CD4 count above 200 cells/mm³. These studies, combined with the opportunistic nature of *Pneumocystis jirovecii* pneumonia, which very rarely affects individuals without severe immune suppression, set the foundation for the existing clinical recommendations for the use of co-trimoxazole for children living with HIV in high-income countries (39,40), where interrupting co-trimoxazole with a CD4 count above 200 cells/mm³ has become clinical practice for almost a decade.

5.3.3 Dosing for children

The dosing of co-trimoxazole prophylaxis for children is optimized based on body weight bands (Annex 2). No robust evidence was identified that would warrant a change to the current dosing recommendations for children (30,31,41).

5.4 Co-trimoxazole prophylaxis for HIV-exposed infants

- Co-trimoxazole prophylaxis is recommended for HIV-exposed infants 4–6 weeks of age and should be continued until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breastfeeding.

(Strong recommendation, very-low-quality evidence)

Several factors since 2006 have warranted new recommendations on the use of co-trimoxazole prophylaxis in HIV-exposed infants, particularly with increasing effectiveness of preventing the mother-to-child transmission of HIV interventions. In settings where the coverage of services for preventing the mother-to-child transmission of HIV and early infant diagnosis are both high, there are questions as to whether co-trimoxazole prophylaxis provides any added benefit for HIV-exposed uninfected infants who are breastfed (42). Nevertheless, higher morbidity and mortality reported for HIV-exposed uninfected infants compared to unexposed infants, including increased susceptibility to *Pneumocystis jirovecii* pneumonia, has been reported (43).

The group considered that the evidence of clinical benefit for HIV-exposed uninfected infants who are not at risk of acquiring HIV infection is insufficient to recommend the use of co-trimoxazole prophylaxis in this population. Although the benefit demonstrated by randomized evidence (44) in reducing malaria incidence was recognized, the Guideline Development Group decided to maintain the existing recommendation in face of alternative interventions (malaria intermittent preventive treatment for infants, bed-nets and pneumococcal and rotavirus vaccine) that are currently being implemented to prevent malaria, pneumonia and diarrhoea among children

without HIV. The existing recommendation was simplified in language, and both the strength of the recommendation and the quality of evidence have now been defined.

Given the rationale for providing co-trimoxazole prophylaxis in breastfed infants who could potentially become infected, the evidence to support this recommendation is derived from the CHAP trial, which demonstrated a benefit in survival for children initiating co-trimoxazole prophylaxis. This evidence was downgraded for indirectness and was considered of very low quality for the use of co-trimoxazole among HIV-exposed infants. However, this intervention is considered safe and extremely valuable during the period with the highest HIV-related mortality in the first 2 years of life. Given the very low coverage of infant testing and the existing challenges in ensuring the timely identification and linkage of infants living with HIV, particularly those acquiring HIV infection during breastfeeding, no major uncertainty in terms of risks, acceptability and feasibility was detected, and the strength of recommendation was thus ranked as strong. In summary, co-trimoxazole prophylaxis should be started for all HIV-exposed infants but not be continued after the period during which HIV-exposed uninfected infants have a risk of acquiring HIV infection.

5.5 Implementation considerations

Some of the major barriers to implementing co-trimoxazole prophylaxis include (a) supply chain and management issues leading to stock-outs; (b) imposing user charges for medication and/or monitoring; (c) inadequate training,

supervision and/or mentoring of health-care workers; (d) low coverage levels of HIV testing and counselling; and (e) lack of coordination across programmes. National programmes could implement co-trimoxazole prophylaxis policy and guidelines more effectively through various mechanisms (Box 5.1).

Box 5.1 How to improve the implementation of policy and guidelines on co-trimoxazole prophylaxis at the national level

- Adapt WHO guidelines to the national context
- Strengthen national and local drug supply management systems to ensure the sustained availability of co-trimoxazole at health care facilities
- Secure funding for providing co-trimoxazole prophylaxis to ensure that no user charges for co-trimoxazole are imposed
- Coordinate with malaria programmes at the country level regarding recommendations related to the intermittent preventive treatment of malaria in pregnancy and seasonal malaria chemoprophylaxis for children younger than 5 years
- Provide co-trimoxazole prophylaxis to eligible people at TB, maternal, newborn and child health and opioid substitution therapy services
- Scale up the training and sensitization of health care workers
- Increase co-trimoxazole prophylaxis knowledge at the community level
- Ensure that a human rights framework is used: for example, people with HIV should always consent to using co-trimoxazole prophylaxis
- Ensure that high-quality co-trimoxazole formulations are provided
- Monitor the toxicity of adverse reactions, particularly in chronic use of co-trimoxazole prophylaxis
- Assess adherence to policies and the impact on population health

5.6 Research gaps

Future research is essential to better understand the long-term safety of and adherence to co-trimoxazole prophylaxis in all populations. Examining barriers to co-trimoxazole prophylaxis adherence into adolescence, and eventually into adulthood, will help optimize the management of HIV infection. Further research is also needed on the benefits and risks among people with high CD4 cell counts receiving ART. For example, the effect of co-trimoxazole prophylaxis for both adults and children receiving ART who then develop TB needs to be examined.

Since introducing co-trimoxazole prophylaxis early to HIV-exposed uninfected infants might cause gut perturbations and affect the gut microbiome, the Guideline Development Group recognized that research could inform how infant immunity is affected. Further, the Guideline Development Group recommended future studies using animal models and clinical studies in humans to address co-trimoxazole toxicity. Future studies are also needed to assess the safety and

appropriate dosing of co-trimoxazole prophylaxis in neonates (<4 weeks of age), for whom co-trimoxazole prophylaxis is not currently recommended because of potential kernicterus. A review of the evidence (45) has shown that co-trimoxazole prophylaxis among neonates is unlikely to cause kernicterus. Animal models and clinical studies could better inform the safety of initiating co-trimoxazole prophylaxis when infants are diagnosed with HIV soon after birth.

More surveillance of co-trimoxazole prophylaxis use during pregnancy and breastfeeding is also required. The Guideline Development Group emphasized the need to measure birth outcomes, birth defects and toxicity in infants. Although the systematic review of dosing studies in adults demonstrated the non-inferiority of lower dose, adequately powered studies are needed to improve confidence in the size of the effect for death and treatment-limiting adverse events. Although co-trimoxazole is well tolerated with low rates of toxicity, skin rash (including Stevens-Johnson syndrome), reactions of the blood and blood-forming organs and liver toxicity have been reported. Future studies could help identify the people at

highest risk of developing hypersensitivity and severe toxicity.

The Guideline Development Group also suggested that future co-trimoxazole research should explore the cost-effectiveness and acceptability among people with HIV (Table 5.1). Although co-trimoxazole has been shown to be effective in settings with high levels of co-trimoxazole resistance, understanding whether people living with HIV using co-trimoxazole affects community co-trimoxazole resistance and whether community

co-trimoxazole resistance affects treatment failure for other infectious diseases is important for national efforts to combat antimicrobial resistance. The use of a fixed-dose combination of co-trimoxazole + isoniazid + pyridoxine should also be explored where large proportions of people living with HIV are eligible for these medications (Table 5.2). Lastly, co-trimoxazole's potential anti-inflammatory properties may have a role in HIV therapy, and this warrants more research (46).

Table 5.1 Criteria for initiating and discontinuing co-trimoxazole prophylaxis

Population	Recommendations	
	Criteria for initiating co-trimoxazole prophylaxis	Criteria for discontinuing co-trimoxazole prophylaxis
Adults (including pregnant women) with HIV	<p>Initiate in everyone with severe or advanced HIV disease (WHO clinical stage 3 or 4) or CD4 \leq350 cells/mm^{3a}</p> <p>In settings with high prevalence of malaria and/or severe bacterial infections^b: initiate for everyone regardless of WHO clinical stage or CD4 cell count</p>	<p>May be discontinued for those who are clinically stable^c, with evidence of immune recovery and/or viral suppression on ART^{d,e}</p> <p>In settings with a high prevalence of malaria and/or severe bacterial infections: should be continued</p>
Children and adolescents with HIV	<p>Initiate for everyone regardless of WHO clinical stage or CD4 cell count</p> <p>As a priority: (1) initiate for everyone younger than 5 years regardless of WHO clinical stage or CD4 cell count; (2) initiate for everyone older than 5 years with severe or advanced HIV disease (WHO clinical stage 3 or 4) or a CD4 count \leq350 cells/mm³</p>	<p>In settings with a high prevalence of malaria and/or severe bacterial infections: should be continued until adulthood</p> <p>In settings with a low prevalence of both malaria and severe bacterial infections: may be discontinued for those older than 5 years who are clinically stable, with evidence of immune recovery^f and/or viral suppression on ART</p>
HIV-exposed but uninfected infants	<p>Initiate for everyone starting at 4–6 weeks after birth</p>	<p>Until the risk of HIV transmission ends or HIV infection is excluded^g</p>
People living with HIV and TB ^h	<p>Initiate for everyone with active TB regardless of CD4 cell count</p>	<p>Until adult or children criteria for discontinuation are met</p>

^a This group is also given priority for ART initiation (as recommended for ART in the 2013 WHO consolidated guidelines (47)).

^b Settings in which malaria and/or severe bacterial infections are highly prevalent include low- and middle-income countries with high rates of mortality for children younger than 5 years old (48).

^c Clinically stable adults are defined as individuals receiving ART for at least 1 year without any new WHO clinical stage 2, 3 or 4 events.

^d CD4 count $>$ 350 cells/mm³, with viral load suppression, is considered immune recovery (some countries may adopt a threshold of CD4 count $>$ 500 cells/mm³).

^e WHO recognizes that, in settings with a low prevalence of malaria and severe bacterial infection settings where co-trimoxazole is used primarily as prophylaxis for some HIV-associated opportunistic infections (*Pneumocystis jirovecii* pneumonia and toxoplasmosis), guidelines exist for discontinuing co-trimoxazole in adults with HIV infection when there is evidence of viral suppression and immune recovery at a CD4 count $>$ 200 cells/mm³ and they have been receiving ART for at least 1 year.

^f Parameter for immune recovery among children $>$ 5 years old: CD4 count $>$ 350 cells/mm³, with viral load suppression.

^g In settings with high malaria transmission, consideration may be given to extending co-trimoxazole prophylaxis among HIV-exposed uninfected infants up to 2 years of age.

^h Recommendation maintained from WHO policy on collaborative TB/HIV policy activities: guidelines for national programmes and other stakeholders (49).

Table 5.2 Simplified dosing of co-trimoxazole prophylaxis for children

Drug	Strength of tablet or oral liquid (mg or mg/5 ml)	Number of tablets or ml by weight band once daily					
		3.0–5.9 kg	6.0–9.9 kg	10.0–13.9 kg	14.0–19.9 kg	20.0–24.9 kg	25.0–34.9 kg
Co-trimoxazole	Suspension 200/40 mg per 5 ml	2.5 ml	5 ml	5 ml	10 ml	10 ml	–
	Tablets (dispersible) 100/20 mg	1	2	2	4	4	–
	Tablets (scored) 400/80 mg	–	0.5	0.5	1	1	2
	Tablets (scored) 800/160 mg	–	–	–	0.5	0.5	1