Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Sulfamethoxazole and Trimethoprim

Biseptol 480
Bactrim

SE/W/0024/pdWS/001

Rapporteur:	Sweden
Finalisation procedure (day 120):	2016-11-30

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VI
INN (or common name) of the active substance(s):	Sulfamethoxazole and Trimethoprim
MAH (s):	See section VI
Pharmaco-therapeutic group (ATC Code):	J01EE01
Pharmaceutical form(s) and strength(s):	Concentrate for solution for infusion, 80mg/ml+16mg/ml and Oral solution, 40mg/ml+8mg/ml Tablets, 400mg/80mg Forte tablets, 800mg/160mg

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 4.1, 4.2, 4.3 and 5.2.

Summary of outcome

☐ No change

☐ New study data: <section(s) xxxx, xxxx>

☐ New safety information: <section(s) xxxx, xxxx>

☒ Paediatric information clarified: mainly section(s) 4.1 and 5.2.

☐ New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION

Type IB/II variation is requested as appropriate. The PI for products with these substances should be updated with missing information in all sections of the PI as appropriate (and data if needed). Other sections *may* be affected (e.g. section 4.4 where changes may be required depending upon changes in section 4.3).Please see section V.

III. INTRODUCTION

Several MAHs submitted a large number of completed paediatric study(ies) for sulfamethoxazole (SMZ) + trimethoprim (TMP), in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

(A short critical expert overview has also been provided.)

The MAH for Bactrim stated that the submitted paediatric studies do not influence the benefit risk for Bactrim and that there is no consequential regulatory action.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing
- An annex including SmPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product, and related PL wording

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

This paediatric procedure covers three different pharmaceutical formulations; a concentrate for solution for infusion, a tablet and an oral solution. Formulations specific to paediatric use are generally not available.

IV.2 Non-clinical aspects>

1. Introduction

None of the MAHs did submit any non-clinical data.

IV.3 Clinical aspects

The studies have been summarized below for each respective MAH.

Roche

1. Introduction

The product Bactrim is available as tablets, syrup or a concentrate for solution for infusion. The indications are respiratory tract and ear infections, urogenital tract infections, gastrointestinal tract infections, other bacterial infections and septicaemia (intravenous infusion only).

The standard dosages for adults and children over 12 years are provided in the table below.

Table 1 Standard dosage for adults and children over 12 years old

	Tablets		Forte Tablets		Measures of syrup	
	morning	evening	morning	evening	morning	evening
Standard dosage	2	2	1	1	4	4
Minimum dosage and dosage for long-term therapy (longer than 14 days)	1	1	1/2	1/2	2	2
High dosage (for particularly severe cases)	3	3	1 1/2	1 1/2	6	6

Source: Clinical overview

The schedules for children are approximately equivalent to a dose of 6 mg TMP and 30 mg SMZ per kg bodyweight per 24 hours and provided in the table below.

Table 2.Normal dosage for children under 12 years of age

Age	Measures of syrup – every 12 hours	
6 weeks to 5 months		$^1/_2$ (2.5 ml)
6 months to 5 years		1 (5 ml)
6 years to 12 years		2 (10 ml)

Source: Clinical overview

Regarding intravenous infusion, the average dosage is approximately 2 ml/5 kg bodyweight daily for children up to 12 years old. Bactrim is contraindicated in the first 6 weeks of life.

Bactrim was first granted a marketing authorization in Austria on 1 April 1969 and was also approved in the European Union on 1 April 1969. As of 31 March 2015, Bactrim has been approved in approximately 100 countries worldwide, including 13 in the EU.

No changes in the currently approved SmPC were proposed by the MAH.

2. Clinical Pharmacology studies

Two of the 9 studies that were included in the line listing in 2008 contain some pharmacokinetic data. The major findings are summarized in Table 3 below.

Table 3. Sulfamethoxazole (SMZ) + trimethoprim (TMP) dosage in children. Roche supported studies

Author	Study design	Diagnosis	Dose (mg) and route of administration	Duration of therapy in days (mean)	Positive Outcome.	
					Clinical	Bacteriological
Dr. L. Havas RAPPORT Nr. 54'340	Dosage scheme, concerning all medicaments, for the treatment of children. Dosage calculated using the body surface area method (and not on the basis of body weight but	Not applicable	Oral. 1 pill contains SMZ 400 mg and TMP 80 mg. Adults (65 kg) = 4 pills = 100% Children: 7 year old (23 kg) SMZ 800 mg and TMP 160 mg (= 50%) 12 year old (40 kg) SMZ 1200 mg and TMP 240 mg (= 75%)	Not reported.	Not applicable	Not applicable
Reggiani G (1973) Rapport No. 52664 U	Controlled clinical trial. 25 hospitalized children aged 10 months to 15 years	Gastroenteritis: • salmonella (13), • shigella (10) • nonbacterial gastroenteritis (2).	Oral. SMZ 100mg and TMP 20 mg /kg/day (divided q6h) The projected steady-state SMZ serum concentration of 168 µg/mL in the adult compares closely with the value of 173.5 µg/mL reported for children.	7 days	**Serum** mean concentration: SMZ free: 173.5 µg/ml, TMP free: 9.6 µg/ml. Mean of the individual **serum ratio** SMZ free/TMP was 23.8/1. **Urine** SMZ + TMP mean concentration: SMZ free: 881 µg/ml (SMZ total: 2026 µg/ml) TMP free: 330 µg/ml Mean of the individual **urine** ratio of SMZ free/TMP	Not applicable

Source: Clinical overview

Rapporteur´s comment:
These two Roche supported studies are related to PK and dose equivalence. Havas et al. aimed to establish body surface area and body weight conversion scheme for paediatric patients. Reggiani et al evaluated safety and PK profile patients with gastroenteritis with 2-5 times the adult dose. They do not add any new information that can be reflected in the SmPC.

Summary of pharmacokinetic literature review

A comprehensive review of the published pharmacokinetic studies was performed and the studies identified, together with the key findings are presented in Table 4 below. An additional study performed in patients with renal impairment has also been identified and this is summarised in Table 5.

Table 4. Clinical pharmacokinetic studies in paediatric subjects

Authors / year	Subjects N° + type / age years	Dosage / Route mg/kg	Cltot Plasma mL/min / (kg)	t1/2 h Plasma	Comments
Ardati 1979	*18 subjects:* 1 newborn (3 weeks); 10 infants 2-18 months; 5 children 4-11 years; 2 adolescents (13 y)	TMP 10 mg/kg SMZ 50 mg/kg iv	Not determined	TMP 5.5 SMZ 8.5	Patients had streptococcus or staphylococcus infections -No specific analysis by age classes - during therapy 13/18 had haematological abnormalities and 9/18 had neutropenia (7 mild, 2 severe) $t_{1/2}$ shorter in paediatrics than that observed in adults -treatment iv over 10 days and po over mean 9 days in 11/18 pts Rational for dose selection not communicated.
Bravo 1984	*17 subjects:* UTI, Burn 2.5 to 24 months 7 malnourished 10 eutrophic	Eutrophic children TMP-SMZ. Oral suspension Dose based on 22 mg/kg SMZ	SMZ 1.38** G+G[1] **Adults** **Cl = 0.32**	SMZ 4.9** G+G[1] **Adults t1/2 = 10.1**	**PK Study on SMZ alone** Comparison 7 malnourished to 10 eutrophic infants. $t_{1/2}$ in normal infants significantly shorter than reported in adults(G+G[1]). Clearance in normal infants significantly larger than in adults (G+G[1]). **Authors' Conclusion:** The study results suggest that a revision in the frequency of the administration of SMZ for infections in malnourished children under prolonged treatment and in patients with extracellular fluid alterations is to be considered.
Hoppu 1984	5 girls with UTI aged 1 to 10 y vs 3 healthy males 26.4 y to 37.3 y	TMP po suspension 6 mg/kg bid during 10 days	**Children** 2.1-2.8 **Adults** 0.4 – 1.2	**Children** 3.0–5.5 **Adults** 9.3 – 13.6	Preliminary study with small number of subjects Study on TMP alone Appropriate study design and conduction for SD PK study. Clear PK difference between children and adults Too small to make a distinction between Child age classes

Authors / year	Subjects N° + type / age years	Dosage / Route mg/kg	Cltot Plasma mL/min / (kg)	t1/2 h Plasma	Comments
Hoppu 1987	*18 Children* with UTI **A** 9 girls 1 to 3.6 y **B** 9 girls 7.5 to 9.7 y 12 healthy adults 27 to 44.6 y	TMP po suspension 3 mg/kg bid during 10 days for therapy Healthy subjects SD 3 mg/kg	**Children** A_{TOT} 2.8* A_R 1.2* A_{NR} 1.4* B_{TOT} 2.4* B_R 0.8* B_{NR} 1.7* **Adults** CL_{TOT} 1.4 * CL_R 0.6* CL_{NR} 0.8 *	**Children** **A** 3.7* **B** 5.4* **Adults** 11.2*	**PK Study on TMP alone** Good study design and conduct for SD PK study. Reasonable number of subjects included. **Results:** CL_{tot} in adults < Children **B** < Children **A** CL_R and CL_{NR} in adults < Children **B** < Children **A** $t_{1/2}$ adults > Children **B** > Children **A** Statistically significant results P< 0.001 **Author's conclusion:** TMP dose should be increased in children - younger Children **A** increase 100%; - older children **B** increase 70%
Hoppu 1989	*6 infants*: 1.7 months to 1.1 year.	2 patients TMP-SMZ iv 1 patient TMP-SMZ po suspension 3 patients TMP po suspension TMP dose 0.61 to 3.52 mg/kg	TMP CL_{TOT} 3.3	TMP 3.8	**PK Study on TMP only** Comparison with published data from new-borns, children and adults. **Author's conclusion** The most dramatic changes in TMP PK seem to occur during the first two months of life. A reduced daily dose of trimethoprim is necessary during the first two months only. An increased daily dose, by addition of a third dose each day, is recommended from two months.
Rylance 1985	*18 Children* UTI aged 3 months to 13 years No attempt to separate age classes. 4 Children < 1 year 4 Children > 9 years 5 Children between 1 and 9 years	SD TMP po 10 mg/kg	4.0	Plasma 6.8 Urine 7.9	**PK Study of TMP only** **SD TMP** The results support a higher clearance and longer $t_{1/2}$ of TMP in children as compared to adults. Different parameters have been determined from urinary excretion.

Authors / year	Subjects N° + type / age years	Dosage / Route mg/kg	Cltot Plasma mL/min / (kg)	t1/2 h Plasma	Comments
Siber 1982	*37 subjects with PJP* Age 0.2 to 82 years 1 patient < 0.25 year 9 patients aged 0.25 year to 9.9 years 14 patients aged 10 to 49 years 4 patients aged > or = 50 years	TMP-SMZ iv Dose: /m^2 TMP 150 + SMZ 750 / m^2 every 8h = 3 x /d	Not determined	Plasma *** x< 0.25 **T** 11.4 **S** 7.5 x 0.25 to 9.9 **T** 5.6 **S** 9.9 x 10 to 49 **T** 9.5 **S** 10.1 x > 50 **T** 16.0 **S** 14.7	$t_{1/2}$ of both TMP and SMZ, was shorter in children than in adults $t_{1/2}$ of both TMP and SMZ, was the largest in elderly. This was the only paper identified, which examined the pharmacokinetics in subjects with PJP including children, adults and elderly. However the age classes are empiric. No distinction of age has been made in the group of subjects aged 0.25 and 9.9 years Globally the results are in agreement with those described in more carefully performed studies (Hoppu 1984-1989). However, the study was performed with TMP-SMZ. The number of patients is high (n = 37) and efficacy and safety have been investigated. In this study it was considered that therapeutic concentrations of TMP should range between 5 to 10 µg/mL during therapy of PJP.

Authors / year	Subjects N° + type / age years	Dosage / Route mg/kg	Cltot Plasma mL/min / (kg)	t1/2 h Plasma	Comments
Springer 1982	*12 new-born infants* -3 days old	TMP-SMZ iv 10 subjects received TMP 5 mg/kg + SMZ 25 mg/kg 1 subject received TMP 10 mg/kg + SMZ 50 mg/kg 1 subject received TMP 3 mg/kg + SMZ 15 mg/kg	**T** 1.8 **S** 0.35	**T** 19.0 **S** 16.5	This represents the only PK study with Bactrim performed in new-borns. The major PK parameters including Cl_{Tot} and $t_{1/2}$ in new-borns were significantly different from that observed in other age groups of the paediatric population. Cl_{Tot} was significantly smaller in new-borns than in adults, while $t_{1/2}$ in new-borns was significantly larger than in adults. These observations support a smaller TMP-SMZ dosage in this paediatric sub-group. **Author's conclusion** Based on these data the recommended loading dose is 3mg/kg TMP and 10 mg/kg SMZ, and the maintenance dose is 1 mg/kg TMP and 3 mg/kg SMZ. The ratio of TMP/SMZ is therefore different from that of the current Bactrim galenic formulations.

1: G+G = Goodman and Gilman

Trimethoprim = TMP; Sulfamethoxazole = SMZ; T = TMP; S = SMZ

* = Mean; Children A age 1 to 3.6 years; Children B age 7.5 to 9.7 years

** = Normally nourished children figures for SMZ alone

*** x = age class; x < 0.25 = below 3 months, 1 subject; x 0.25 to 9.9 = from 0.25 y to 9.9 y, 9 subjects; x10 to 49 = from 10y to 49 y 14 subjects; x > 50 = more than 50 years 4 subjects

Pharmacokinetic studies in newborn infants (0 to 27 days)

Springer 1982:

The pharmacokinetics of TMP-SMZ was determined in 12 newborn infants aged less than 3 days following single or repeated iv administration. The patients had Klebsiella pneumonia resistant to kanamycin and gentamicin and normal renal function. The mean t1/2 was 16.5h for SMZ and 19h for TMP. The mean total body clearance was 0.65 mL/min for SMZ and 3.31 mL/min for TMP. Based on these data, the authors recommend a loading dose of 10mg/kg SMZ and 3mg/kg TMP and a maintenance dose of 3mg/kg SMZ and of 1mg/kg TMP. No AEs were observed during the treatment.

Pharmacokinetic studies in infants and toddlers (28 days to 23 months)

Bravo 1984 :

The pharmacokinetics of TMP-SMZ was examined in seven malnourished (marasmic) infants receiving treatment for urinary tract infection. Comparisons were made with the SMZ level of ten nutritionally normal infants, hospitalized for first and second degree burns, receiving CMZ for treatment of bronchitis. TMP-SMZ was administered as an oral suspension (20 mg TMP and 100 mg SMZ, 5 mL), patients receiving 22 mg SMZ/kg body weight. Capillary blood samples, 0.05 mL were taken at prescribed intervals. Elimination half-life of SMZ in the marasmic infants was prolonged as compared to in their eutrophic counterparts, 9.6 vs 4.9 h. In addition, the SMZ total body clearance 1.38 mL/min/kg in eutrophic patients was larger compared to the malnourished infants 0.68 mL/min/kg.

Hoppu 1989 :

The pharmacokinetics of trimethoprim alone, administered orally or intravenously were investigated in six infants aged 1.7 month to 12.1 months. In these infants TMP had a mean half-life of 4.6 hours; this was slightly smaller than the mean value. of 5.4 hours found in children aged 8 to 10 years. The plasma clearance in the infants (3 3 ml/min/kg) was slightly larger than in children (2.9 ml/min/kg).

Compared to the pharmacokinetic results observed in new-borns (Springer 1982) it can be observed that the most dramatic changes in trimethoprim pharmacokinetics seem to occur during the first two months of life. A reduced daily dose of trimethoprim is necessary during the first two months only. An increased daily dose, by addition of a third dose each day, is recommended from two months.

Summary:

Both studies demonstrated that, in infants below 23 months and older than 2 months, the elimination half-lives of TMP and of SMZ are shorter than those observed in older children or in adults. In this population, the total body clearance of both TMP and SMZ is higher as compared to older children and adults.

Pharmacokinetic studies in children (2 to 11 years)

Hoppu 1984

In this preliminary study, the pharmacokinetics of trimethoprim was investigated in 5 girls with urinary tract infection (UTI) aged 1 to 10 y and compared to that in 3 healthy male subjects. All subjects received a 6 mg/kg/d dose administered orally as a TMP suspension. The results although preliminary showed that t1/2 of TMP was shorter and total body clearance larger in the children compared to adults.

Hoppu 1987 :
The pharmacokinetics of trimethoprim was studied in children (nine girls 1.05 to 3.57 years old and nine girls 7.55 to 9.70 years old) with urinary tract infections and 12 healthy adults (27.07 to 44.62 years old) to investigate any age-related changes. Serum and urine concentrations were measured during 24 hours. The groups did not differ in the time or the height of the peak serum concentration. Thereafter the children had lower serum concentrations. Children had a shorter elimination half-life (means: 1 to 3 years, 3.7 hours; 8 to 10 years, 5.4 hours; adults, 11.2 hours), and higher total clearance (2.8 mL/min/kg; 2.4 mL/min/kg; 1.4 mL/min/kg) as compared to adults. The higher clearance in children was mainly non-renal (metabolism). The author concludes that the size of the single daily TMP dose should be related to age and the infection treated; 3 mg/kg being probably sufficient for treatment of urinary tract infections Calculation of the pharmacokinetic variables per unit of body surface area modified the age differences considerably.

Siber 1982:
In this study thirty-seven children and adults with infection, aged 0.2-82 years were treated intravenously with 150 mg of trimethoprim (TMP) and 750 mg of sulfamethoxazole (SMZ)/m2 every 8 h, usually for known or suspected Pneumocystis jirovecii pneumonia. When necessary, dosage was adjusted to maintain peak TMP levels of 5-10 ug/mL. On day 2 of treatment, mean peak levels of TMP-SMZ were 7.02 and 148 µg/ml, respectively, and mean half-lives were 9.6 and 10.7 h, respectively. Serum concentrations of N4-acetylSMZ, the major hepatic metabolite of SMZ, increased in proportion to concentrations of creatinine in serum ($r = + 0.92$; $P < 0.001$). Adverse effects included fluid overload due to the large dilution volume and thrombocytopenia, which was associated with higher serum TMP levels and longer treatment as compared with non-thrombocytopenic patients. A loading dose of 250 mg of TMP and 1,250 mg of SMZ/m2 is recommended, followed by maintenance doses of 150 mg of TMP and 750 mg of SMZ/m2 every 8 h for children aged 10 years or younger and every 12 h for adults with normal renal function. In the children population aged 0.25 to 9.9 y the elimination half-lives of TMP and SMZ were shorter as compared with that observed in older patients' groups.

Pharmacokinetic studies in adolescents (12 to 16-18 years (dependent on region))
No study investigating the pharmacokinetics of TMP and /or SMZ has been performed in adolescents

Rapporteur´s comment:
The pharmacokinetic data in children seem to be adequate even if some studies are small; other has included enough number of individuals to get a good understanding of the pharmacokinetics. The data in general indicates that the half-lives for TMP and SMZ in children are shorter than in adults and that clearance are higher however with the exception of new-borns. In new-borns (below 27 days) the mean t1/2 was 16.5h for SMZ and 19h for TMP. In healthy infants (28 days to 23 months) the half-life was 4.9 h for SMZ and 4.6 h. In older children between 2 to 11 years the mean half-lives of TMP was 3.7 hours in 1 to 3 years, and 5.4 h in 8 to 10 years. In adults the half-life was around 11h. In older children the mean half-lives of SMZ was around 9h and in adults it is longer.

There are treatment recommendations for children down to 6 months of age. The doses in children are lower than the adult doses. This is not in accordance with the pharmacokinetic difference seen for children vs adults which would rather suggest that higher doses would be used. However this will not be questioned. However the MAH is asked to update section 5.2 with the pharmacokinetic information especially the half-life in the different age groups that is included in the posology recommendation.

The current Swedish SmPC text in section 5.2
Paediatric population

In children between 1 and 9 years, the total plasma clearance of trimethoprim is about three times larger than in adults. As a consequence the half-life in children less is than half of that observed in adults.

Table 5. Clinical pharmacokinetic study in paediatric subjects with renal impairment

Authors / year	Subjects N° + type / age years	Dosage / Route mg/kg	Cltot Plasma mL/min / (kg)	t1/2 h Plasma	Comments
Hoppu 1987	*14 children* (two neonates 1 week and 3.7weeks, 2 children < 1 year, 3 children between 1 and 2 years, 1 child of 6.5 years and 6 children > 10 years **with renal insufficiency.** **Mean age 7 years Range: 1 week to 16.4 years**	Single Dose of TMP po Suspension Range 0.3 mg/kg to 3.1 mg/kg. Most patients 9/14 received a dose of 3 mg/kg			PK of TMP was investigated in children with severe renal insufficiency. The half-life (t1/2) of TMP was inversely related to the GFR. The slower elimination rate was mainly the result of lowered renal clearance of TMP. Decreased renal function leads to slower CL_R of TMP, slower CL_{Tot}, and a longer t1/2. **Author's conclusion** The authors recommend reduced daily doses of TMP if the GFR is <30 ml/min/1 73 m^2. The reduction should be proportional to the reduction in GFR and primarily take the form of a prolonged dose interval.

Hoppu 1987:
The pharmacokinetics of trimethoprim were investigated in 14 children (two neonates) with renal insufficiency. Subjects were aged 1 week to 16.4 years old and had glomerular filtration rates (GFR) between 10.8 to 72.3 ml/min/1.73 m2. The half life (t1/2) of trimethoprim was inversely related to the GFR. The slower elimination rate was mainly the result of lowered renal clearance of trimethoprim.
In some individuals the pharmacokinetics of trimethoprim deviated from that expected from the GFR. The authors recommend reduced daily doses of trimethoprim if the GFR is <30 ml/min/1.73 m2. The dose reduction should be proportional to the reduction in GFR and be primarily based on prolongation of the dose interval.

Rapporteur´s comment:
In the current SmPC text section 5.2 this text (or similar) is included regarding children and reduced renal function:
In children with renal insufficiency (CLcr < 30 mL/min) the clearance of TMP is reduced and its elimination half-life prolonged. Therefore the TMP-SMZ dose should be reduced proportionally to the decrease in GFR in this patient population.
This is considered acceptable; however there should be cross-reference to Section 4.2.

3. Clinical studies

Of the ten Roche supported studies submitted, two involved pharmacokinetic data. The remaining eight studies are presented in this section, focusing on efficacy and safety data. For clarity, the studies are presented in the following tables and comments are given below.

➢ Methods

The overall description of the submitted clinical studies are shown below together with the efficacy outcome. The safety is presented in a subsequent section below.

- Study design
  Of the 10 studies submitted, five were uncontrolled and three were comparative studies. The studies were generally single-blind or open.

- Study populations
  Male and female children and adolescents in the age range of 3 months to 14 years were included in the studies. The indications for treatment were otitis media (7 studies), sinusitis (5 studies), lower respiratory tract infection (5 studies, including bronchitis), urinary tract infection (4 studies), tonsillitis/pharyngitis (4 studies) and lymphadenitis (1 study).

- Treatments
  The SMZ-TMP doses used in the studies were within the range of the recommended dosage. The duration of treatment varied between 2 and 17 days. Reference treatment was ceftriaxone in the three comparative studies.

- Outcomes/endpoints
  Clinical and bacteriological outcome were used for assessment of efficacy.

➢ Results

- Efficacy results

Efficacy results are summarized in Table 4 below.

Table 4. Description of clinical studies

Author	Study design	Diagnosis	Dose (mg) and route of administration	Duration of therapy in days (mean)	Positive Outcome (N[%] pts)	
					Clinical	Bacteriological
Braunsteiner A (Research report B 115'427)	Open, uncontrolled study	Acute bacterial infections • otitis media (19) • Sinusitis (1) • LRTI[1] (9) • UTI[2] (1) range in age from 1 to 10 years with a mean of 4.0 years	SMZ[3] 30 mg TMP[4] 6 mg/kg bw/day, per os	3 to 10 days (7.4 days)	30/30 [100%]	No information available regarding microbiology
Braunsteiner A (Research report B 115'428)	Open, uncontrolled study	Acute bacterial infections • Tonsillitis (28) • Otitis media (5) • Sinusitis (1) • Bronchitis (15) • UTI (1) range in age from 1 to 12 years with a mean of 4.7 years	SMZ 30 mg/TMP 6 mg/kg bw/day, per os	2 to 8 days (5.9 days)	48/50 [96%]	No information available regarding microbiology

Braunsteiner A (Research report B 115'429)	Open uncontrolled study	Acute bacterial infections • Tonsillitis/pharyngitis (28) • Otitis media (5) • Sinusitis (1) • Bronchitis (15) • UTI (1) range in age from 1 to 10 years with a mean of 3.1 years	SMZ 30 mg TMP 6 mg/kg bw/day per os	2 to 11 days (7.3 days)	27/29 [93%]	No information available regarding microbiology
Braunsteiner A (Research report B 115'430)	Open, uncontrolled study	Acute bacterial infections • Pharyngitis (30) • Sinusitis (2) • Bronchitis (20) ranged in age from 1 to 10 years with a mean of 6.2 years	SMZ 30 mg TMP 6 mg/kg bw/day per os	6 to 10 days (8.5 days)	52/52 [100%]	No information available regarding microbiology
Braunsteiner A (Research report B 115'431)	Open, uncontrolled study	Acute bacterial infections • Tonsillitis/pharyngitis (7) • Otitis media (8) • Sinusitis (1) • Bronchitis (9) • UTI (2) • lymphadenitis (2) ranged in age from 1 to 7 years with a mean of 3.1 years	SMZ 30 mg and TMP 6 mg/kg bw/day per os	2 to 17 days (9.6 days)	29/29 [100%]	No information available regarding microbiology
Cunningham M., (1996) Manuscript No N-136304	prospective, randomized, single-blind, parallel-group, investigator-initiated, single-center, comparative study.	Acute otitis media • CEF: 295 Pts treated • **TMP-SMZ**: 301 Pts treated ranged in age from 3 – 97 months	CEF 50 mg/kg IM, single injection **SMZ** 40 mg **TMP** 8 mg/kg bw/day per os b.i.d. (SMZ + TMP used as a comparator)	CEF: single dose **TMP-SMZ**: 10 days	**Clinically cured patients:** At week 2: CEF = 122/204 [60.4%] **TMP-SMZ** = 136/219 [62.1%] At week 4: CEF = 79/198 [39.9%] **TMP-SMZ** = 101/218 [46.3%]	Nasopharyngeal samples were collected for culture. Microbiological data obtained from these cultures were not included in this report
Cunningham M., (1996) Manuscript No N-136462	prospective, parallel-group, single-center, comparative study	Acute otitis media 203 patients • CEF: ○ 101 randomized patients ○ 53 nonrandomized patients • **TMP-SMZ**: ○ 49 randomized patients range in age from 5-55 months	Ceftriaxone 50 mg/kg IM, single injection Bicillin C-R IM (600,000 U for patients < 10 kg; 900,000 U for patients > 10-15 kg; 1,200,000 U for patients > 15-20 kg) and SMZ 50 mg and TMP 10 mg/kg bw/day per os. b.i.d. (SMZ + TMP used as a comparator).	Ceftriaxone: single dose Bicillin C-R single dose + TMP-SMZ[5]: 10 days oral course	**Clinically cured randomized patients:** At week 2: CEF = 41/60 [68%] **TMP-SMZ** = 35/48 [73%] At week 4: CEF = 30/58 [52%] **TMP-SMZ** = 21/46 [46%]	By patient bacteriologic cure for: *S. pneumoniae, H. influenzae and M catarrhalis*[6] At day2-3: CEF = 83 [95%] **TMP-SMZ** = 29 [85%]
Milne F and Gallimore B (1989) Research report No CA 119'517	Randomized, double blind, comparative study	Acute otitis media 210 completed patients • 105 pts treated with ceftriaxone • 105 pts treated with TMP-SMZ range in age from 1 to 14 years	**SMZ+TMP** p.o./b.i.d. • up to 10 kg: SMZ 200 mg; TMP 40 mg • 10 to 14 kg: SMZ 300 mg and TMP 60 mg • 15 to 24 kg: SMZ 400 mg and TMP 80 mg • 25 to 32 kg: SMZ 600 mg and TMP 120 mg Amoxicillin t.i.d.: 40 mg/kg/day	**TMP-SMZ:** 10 days Amoxicillin: 10 days	**TMP-SMZ:** clinical response to treatment is 86.1% (64.4% cured and 21.8% improved) Amoxicillin: clinical response to treatment is 87.5% (57.6% cured and 29.8% improved)	No information available regarding microbiology

Cure or clinical improvement was reported for the majority of patients in the studies. In the only study where bacteriological outcome was assessed and included in the present report, 95 % of patients treated with ceftriaxone and 85 % treated with SMZ+TMP obtained bacteriological cure at day 2-3.

Rapporteur´s comment:

The Rapporteur agrees with the MAH that the clinical benefit of SMZ+TMP therapy is in line with current SmPC labelling.

All the conditions treated in the studies are among the already approved indications in the SmPCs. Overall, the results from the Roche supported studies are acceptable and present a high percent of positive clinical outcome after treatment with SMZ+TMP. Consequently, the results of the submitted studies support the indications already listed in the SmPCs.

Based on the results from the studies discussed above, SMZ+TMP was found to be equally effective and safe as ceftriaxone in the treatment of acute otitis media and had a high percentage of positive clinical outcome. However, considering the widespread resistance against SMZ+TMP, the Rapporteur is of the opinion that AOM should not primarily be treated with Bactrim.

Bactrim is approved from 6 weeks of age in most countries. The MAH supported studies were performed in children aged 3 months to 14 years, thus being within the already approved age range.

- Safety results

The results from each study are presented in more detail below.

Braunsteiner 1985 (Study 115 427): All 30 cases were evaluable. Acceptability was rated as being “very good” or “good” in 28 patients. The taste of the syrup resulted in 2 patients discontinuing treatment. Gastric tolerance was rated as being good with 1 patient reporting vomiting which resulted in discontinuation of treatment on day 5. Two patients developed adverse reactions whilst being treated (skin rash and vomiting). The adverse reactions observed were consistent with those observed using other formulations of SMZ + TMP.

Braunsteiner 1985 (Study 115 428): All 50 cases were evaluable. Acceptability was rated as being “very good” or “good” in all 50 patients. Gastric tolerance was rated as being very good with 1 patient reporting gastric pain. Four patients developed adverse reactions whilst being treated (skin rash in 3 patients and gastric pain in 1 patient). Two patients discontinued treatment (1 rash, 1 gastric pain). The adverse reactions observed were consistent with those observed using other formulations of SMZ + TMP.

Braunsteiner 1985 (Study 115 429): All 29 cases were evaluable. Acceptability was rated as being “very good” or “good” in 22 patients. Gastric tolerance was rated as being very good in 27 patients. Two patients developed adverse reactions whilst being treated (vomiting in 1 patient and gastric pain in 1 patient). One patient discontinued treatment (1 vomiting). The adverse reactions observed were consistent with those observed using other formulations of SMZ + TMP.

Braunsteiner 1985 (Study 115 430): All 52 cases were evaluable. Acceptability was rated as being “very good” or “good” in all 52 patients. Gastric tolerance was rated as being very good in all 52 patients. There were no reported adverse reactions.

Braunsteiner 1985 (Study 115 431): All 29 cases were evaluable. Acceptability was rated as being “very good” in 28 patients. Gastric tolerance was rated as being very good or good in 28 patients. Four patients developed adverse reactions whilst being treated (vomiting in 2 patients and skin reactions in 2 patients). Three patients discontinued treatment (1 vomiting

and 2 skin reactions). The adverse reactions observed were consistent with those observed using other formulations of SMZ + TMP.

Cunningham et al 1996 (Study 136 304): A total of 480 adverse events were reported from both treatment arms in 263 patients (139 patients treated with ceftriaxone and 124 patients treated with SMZ + TMP). The most common adverse events in patients treated with SMZ + TMP were diarrhoea, irritability and nasal discharge. In patients treated with ceftriaxone the most common adverse events were diarrhoea, diaper rash and rash. One patient from each treatment arm experienced a serious adverse event. None of the adverse events were related to the study treatment. In conclusion ceftriaxone and SMZ + TMP showed equivalence in safety in this study.

Cunningham et al 1996 (Study 136 462): The rate of adverse events was similar between the groups, 77% of patients treated with ceftriaxone and 78% with pen/SMZ + TMP experienced an adverse event. In both groups the most common adverse events were diarrhoea and diaper rash. Three patients experienced serious adverse events but none were considered to be related to the study drugs.

Milne and Gallimore 1989 (Study 119517): No significant differences in safety were found between the two groups. Adverse events were reported in 17.8% of SMZ + TMP treated patients compared to 11.6% of patients treated with amoxicillin. In both groups the most common adverse events were gastrointestinal events and skin rashes. Treatment was discontinued as a result of adverse events in 3 patients in each group. There were no serious adverse events in either group. In conclusion there were no significant difference between SMZ + TMP and amoxicillin in terms of safety.

Rapporteur's comment:

In summary, the incidence of AEs was rather similar for SMZ+TMP and the reference treatment groups. Skin rash and gastrointestinal events are not unknown events and already labelled. The safety data from the studies submitted did not raise any concern of new safety signals.

Overall, the safety profile for SMZ+TMP is well known and no new concerns are identified in children.

Rapporteur´s overall comment on the clinical studies

The paediatric SMZ+TMP doses used in the 8 Roche sponsored studies are within the range of the recommended dosage in the SmPC. Moreover, the clinical benefit of treatment with SMZ+TMP is in general in line with current SmPC labelling, based on the results from the Roche supported studies.

Based on the results from the MAH sponsored studies, SMZ+TMP was found to be equally effective and safe as ceftriaxone in the treatment of acute otitis media and had a high percentage of positive clinical outcome. However, considering the widespread resistance situation against SMZ+TMP, the Rapporteur is of the opinion that AOM should not primarily be treated with Bactrim.

4. Summary of literature

➢ Methods

A systematic literature search was conducted on the electronic databases BIOSIS Previews®, Derwent Drug File, Embase®, Embase® Alert and Medline® and the Cochrane Library. The literature search covered the time period of 1 January 2005 to 28 September 2015. The search terms were keywords from MeSH and Emtree thesaurus for clinical studies, clinical trials, efficacy, effectiveness combined with the drug term Bactrim including synonyms and the age group 0-12 years (the recommended dosing for children over the age of 12 years is the same as that for adults). A free text search in title and abstract with those terms was also performed. Exclusion criteria were letters, editorials, notes, preclinical studies and non-English publications. From the 206 publications identified, only randomized clinical trials with at least 50 patients, observational studies, meta-analyses, and guidelines were considered for the approved indications and off-label use.

Based on these criteria, 37 clinical studies, 3 meta-analyses, 3 systematic reviews, and no guidelines providing supportive evidence for the efficacy of Bactrim in infants and children qualified for inclusion in this document. However, an additional search for guidelines was performed for each indication and yielded 27 relevant guidelines.

Literature related to SMZ + TMP clinical outcome in children by indication is presented in Table 5 (labelled and off-label indications).

➢ Results

Table 5. Clinical outcome in children treated with SMZ+TMP, from published data

Author	Study design	Diagnosis	Dose (mg) and route of administration	Duration of therapy in days (mean)	Positive Outcome (N[%] pts)	
					Clinical	Bacteriological /Parasitological
Labelled Indications						
Respiratory Tract Infection						
Lower Respiratory Tract Infection						
Awasthi, S (2008)	Cluster randomized, open labelled trial	Non-severe pneumonia in children aged 2-59 months of age (2009 cases were randomized)	Oral amoxicillin (125 mg) and SMZ + TMP (20 mg TMP, twice daily)*	3 days of amoxycillin and 5 days of SMZ + TMP	Clinical failure on amoxycillin and SMZ + TMP on intention to treat analysis was 137 and 97, respectively (absolute difference = 0.04, 95% CI: -0.035-0.12). Authors concluded no difference in effectiveness between the two treatments	Not reported
Noorani, QA (2006)	Observational study in Northern Pakistan in respiratory tract infections	Non-severe pneumonia (N = 949 children aged from 2 to 59 months)	Oral SMZ + TMP (4 mg TMP per kg body weight twice daily)*	Not reported	839/944 (88.9%) cases of pneumonia resolved clinically 110 (11.6%) failed therapy; clinical failure significantly higher in children with fast respiratory rate (OR 3.0, 95%CI 1.2–7.6, P = 0.004)	Not reported
Rasmussen, ZA (2005)	Randomized controlled multicenter trial in	Childhood pneumonia in Pakistan	Oral. 4 mg TMP and 20 mg SMZ/kg (normal dose) or 8 mg TMP plus 40 mg	5 days	Treatment success was similar in the standard dose and	Not reported

	respiratory tract infections	1143 children aged from 2 to 59 months	SMZ/kg b.i.d. (double dose)		double dose groups: 466 children in standard dose group (80.6%) and 438 in the double dose group (78.8%) (RR = 1.10; 95% CI = 0.87–1.37)	
Otitis Media						
Soley, C (2007)	Open-label, double tympanocentesis, single-center study in OM	89 children with acute OM were enrolled and received SMZ + TMP (aged 3 to 48 months)	Oral SMZ + TMP twice daily (40 mg/kg/d)	10 days	Bacteriologic eradication was achieved in 80% of children (42 of 52 clinically and bacteriologically evaluable), and overall clinical response at the end of therapy was 78%. Authors concluded that SMZ + TMP clinical response was unsatisfactory, especially among culture-positive children	The eradication rate was poor for *S. pyogenes* (25%) and marginal for *S. pneumoniae* (84%). There were too few patients with *H. influenzae* (100%) and *M. catarrhalis* (100%) to assess effectiveness
Van der Veen, EL (2007)	Randomized, placebo-controlled trial in OM in Costa Rica	101 children aged from 1 to 12 years with chronic active otitis media.	Oral SMZ + TMP (18 mg/kg, b.i.d.)* or placebo All patients received a short course of steroid and antibiotic eardrops	6 to 12 weeks	6 weeks: 28% and 53% of children in the SMZ + TMP and placebo groups, respectively, had signs of otorrhea 12 weeks, 32% and 47%, in the TNP/SMZ and placebo groups, respectively, had otorrhea. At 1 year, otorrhea was similar in the treated and placebo groups (25% and 20%, respectively)	Not reported
van der Veen, EL (2009)	Randomized, double-blind, placebo-controlled trial OM	Chronic active otitis media The effect of SMZ + TMP on the proportion of children with integron-positive and (multi) drug-resistant Enterobacteriaceae in their intestinal tract was studied (99 children aged from 1 to 12 years)	Oral SMZ + TMP 18 mg/kg b.i.d.*	6-12 weeks; medication initially given for 6 weeks, followed by a further 6 weeks if otorrhoea was present at 6 week follow-up visit.		At 6 and 12 weeks follow-up, respectively, in Enterobacteriacea-positive cultures: 32 (91%) and 24 (67%) were resistant to SMZ + TMP in the SMZ + TMP group vs 10 (21%) and 8 (17%) in the placebo group. Multidrug resistance was present in 34 (97%) and 26 (72%) of cultures in the SMZ + TMP group vs 23 (49%) and 26 (55%) in the placebo group.
PJP						
Agrawal, AK	Retrospective	*Pneumocystis jirovecii*	Oral SMZ + TMP	649	No reports of PJP	Not reported

(2011)	chart review	pneumonia (PJP) (87 paediatric patients with an average of 7 years [SD 4.7 years]).	(150/750mg/m^2/day) divided b.i.d. on 2 consecutive days of the week	patient-days		
Bwakura-Dangarembiz, M (2014)	Open-label, randomized, parallel-group, non-inferiority trial	HIV-infected children and adolescents (≥3 years old) on antiretroviral therapy (ART) receiving SMZ + TMP, prophylaxis for bacterial and protozoal infections	758 participants were randomly assigned to stop (n = 382) or continue SMZ + TMP (n = 376) after receiving ART for a median of 2.1 years. SMZ 200 mg q.d. and TMP 40 mg of q.d. (Bodyweight 5-15 kg)* or SMZ 400 mg q.d. and TMP 80 mg of q.d. (15-30 kg)* or SMZ 800mg q.d. and TMP 160 mg q.d. (> 30 kg)* (route not reported)	Long-term prophylaxis (510 days)	: 49 and 21 events of malaria hospitalization occurred in the stopped and prophylaxis-continued groups, respectively Hospitalization for other infections (particularly pneumonia, sepsis, and meningitis): 53 and 25 events in the stopped and prophylaxis-continued groups, respectively	Not reported
Caselli, D (2014)	Prospective survey in PJP	PJP (2466 paediatric patients aged up to 14 years)	TMP (5mg/kg/day divided b.i.d.)/SMZ on 3 consecutive days of the week or TMP (10mg/kg/day divided b.i.d.)/SMZ on 2 consecutive days of the week or TMP (5mg/kg/day divided b.i.d.)/SMZ on 2 consecutive days of the week	Not reported	2 cases of PJP (0.08%)	Not reported
			or TMP (10mg/kg/day divided b.i.d.)/SMZ q.w. or TMP (5mg/kg/day divided b.i.d.)/SMZ q.w. (Oral route)			
Church, JA (2015)	Review of PJP in HIV	Prophylaxis prior to ART, protection against malaria and severe bacterial, prophylaxis in infants exposed to HIV infections. South African study 105 children aged < 2 years; PACTG trial children aged from 2 to 6 years and > 6years; Arrow study 758 children aged > 3 years	Not reported	Not reported	Children in developing countries receiving long-term ART benefit from SMZ + TMP prophylaxis SMZ + TMP provides protection against malaria and non-malaria infections after immune reconstitution in ART-treated individuals in sub-Saharan Africa SMZ + TMP prophylaxis is recommended for HIV-exposed infants from age 4-6 weeks; however, the risks and benefits of SMZ + TMP during infancy are unclear	SMZ + TMP was effective for the reduction of pneumonia in a trial in Zambia despite local resistance rates of 61% among *S. pneumoniae* In Uganda, despite diarrhoea-pathogen resistance of 83%, SMZ + TMP significantly reduced diarrhoea (HR 0·65, 95% CI 0·53-0·81; $P < 0·0001$).
Hughes, WT	Randomized,	Serious bacterial	Atovaquone-azithromycin	Median	Estimated rates of	Not reported

(2005)	double-blind, placebo-controlled trial Serious infections (grouped under the most common infection respiratory)	infections in HIV-infected children (N = 366 [of initial 369] aged 3 months to 19 years)	(atovaquone, 30 mg/kg qd; azithromycin, 5 mg/kg qd) or TMP + SMZ (TMP, 5 mg/kg qd; SMZ, 25 mg/kg qd) * (Route not reported)	durations of follow-up in the intent-to-treat analyses: 160 wk (~3.1 y) and 163 wk (~3.1 y) for the atovaquone - azithromycin and TMP + SMZ groups, respectively.	serious bacterial infection-related events, atovaquone-azithromycin vs TMP-SMZ groups, respectively: 17.3 vs. 24.2 events per 100 patient-y; difference, 6.9 events per 100 patient-y; 95% CI, −0.22 to 14.12 Rates for all end points, atovaquone-azithromycin vs TMP + SMZ groups, respectively: 19.7 vs 27.7 events per 100 patient-y; difference, 7.9 events per 100 patient-y; 95% CI, −0.28 to 15.54 events per 100 patient-y	
Green, H (2007)	Meta-analysis of 12 randomized controlled trials In PJP	*Pneumocystis jirovecii* pneumonia (PJP) in immunocompromised non-HIV-infected patients (1245 patients; 50% paediatric age not reported)	Trimethoprim-sulphamethoxazole (SMZ + TMP) (Various oral doses)	[Variable]	91% reduction was observed in the occurrence of PJP (n = 407; RR, 0.09; 95% CI, 0.02-0.32) Pneumocystis pneumonia-related mortality was significantly reduced (n = 701; RR, 0.17; 95% CI, 0.03-0.94)	Not reported
Lindemulder S and Albano E (2007)	Retrospective chart review of PJP	PJP 482 (345 leukemia, 137 lymphoma) paediatric oncology patients (age not reported)	SMZ + TMP 5 mg/kg/day of TMP divided into 2 doses on 2 consecutive days per week (Route not reported) Dosages was adjusted for growth throughout the prophylaxis	Median 605.5 days	Two noncompliant patients developed *P carinii* pneumonia. There were no cases in compliant patients The median proportion of neutropenic days were similar with SMZ + TMP (0.029) and on the alternative drugs (0.022; pentamidine or dapsone in 34/47 cases)	Not reported
Stern, A (2014)	Cochrane Review	PJP 1412 patients (520 children with acute lymphoblastic leukemia) 60 children median age 4.5 to 5 years; 160 children median age 6 to 6.5 years and 167 children (age not reported).	Various oral doses across 13 trials	Various durations across 13 trials	Compared to no treatment or treatment with fluoroquinolones there was an 85% reduction in the occurrence of PJP in patients receiving prophylaxis with SMZ + TMP, RR of 0.15 (95% CI 0.04 to 0.62; 10 trials, 1000 patients)	
Zar, HJ (2006)	Prospective dose-escalation study in PJP	PJP prophylaxis in HIV-infected children (15 children aged from 11	Oral loading dose of 5 mg/kg, 10 mg/kg or 20 mg/kg TMP (in a suspension of 40 mg TMP	Loading dose with or without	Therapeutic serum TMP concentrations were obtained with a 20	Not reported

		to 40 months)	and 200 mg SMZ per 5 ml of Cozole suspension) those who received a 20 mg/kg dose of TMP were randomised to receive a second dose of either 5 or 10 mg/kg TMP 6 hours after the loading dose	subsequent second dose	mg/kg loading dose at 3 and 6 hours (median [25th percentile – 75th percentile]: 7.68 (6.1-7.8) µg/ml and 6.74 (6.4-6.8) µg/ml, respectively). In patients who received a loading dose of 20 mg/kg TMP, followed by a second dose of 5 or 10 mg/kg, serum TMP levels were maintained in a therapeutic range (6.98 (3.4-8.8) µg/ml and 9.25 (8.2-10.3) µg/ml, respectively).	
Zar, HJ (2010)	Prospective randomized controlled study. Intermittent compared with daily SMZ + TMP preventive PJP therapy	PJP prophylaxis in HIV-infected children (324 children, median age 23 months followed for 672 children-years)	HIV-infected children aged at least 8 weeks were randomized to thrice weekly or daily SMZ + TMP TMP (5 mg/kg of TMP) preventive therapy (Route not reported)	5-year period	Intermittent therapy was associated with more invasive bacterial disease than daily therapy (bacteremias incidence rate ratio 2.36 [95% CI 1.21-4.86]), but survival was similar.	*Streptococcus pneumoniae* was the predominant Gram-positive pathogen (15 infections, 32%) within the 47 incidents of bacteremia
Urinary Tract Infection						
Craig, JC (2009)	Multicenter, prospective, randomized, placebo-	Urinary tract infection (576 paediatric patients) Age / Number of	Oral SMZ + TMP (2/10 mg/kg or 0.25 ml of suspension [containing TMX 40 mg and SMZ 200 mg per 5 ml] /kg, to	365 days	UTI developed in 36/288 [13%] in the SMZ + TMP group and in	*Escherichia coli* was the causative bacterium in 30/36 [83%
	controlled, double-blind clinical trial	(year) / children 0 to < 0.5 / 114 0.5 to < 1 / 148 1 to < 2 / 101 2 to < 4 / 84 4 to < 10 / 117 10 to < 15 / 10 > 15 / 2	the nearest 0.5 ml) single dose q.d. or Placebo		55/288 [19%] in the placebo group	46/55 (84%)]
Falakaflaki, B (2007)	Prospective randomized trial in UTI	Recurrent urinary tract infections (132 paediatric subjects: 96 girls, 36 boys, mean age 3.8 years)	SMZ + TMP (2 mg/kg/day of TMP)* or 1-2 mg/kg/day nitrofurantoin (Route not reported)	6 months	Rate of recurrence: nitrofurantoin, 17 (36.2%); SMZ + TMP, 30 (63.8%), p = 0.029 In children 1-5 y: SMZ + TMP, 16/39 (41%); nitrofurantoin, 7/39 (17.9%) ($P = 0.046$)	*E. coli* was the prominent cause of recurrence in 75% of treated subjects; resistance of nitrofurantoin and SMZ + TMP to *E. coli* was 50% and 52.9%, respectively.
Hari P (2015)	Randomized, placebo-controlled trial In UTI	Urinary tract infection (UTI) and renal damage in children aged 1-12 years with primary vesicoureteric reflux (VUR)	SMZ + TMP 2 mg/kg q.d TMP q.d.)* or placebo (Route not reported)	12 months	10 (21.3 %) on antibiotic prophylaxis 3 (6.5 %) on placebo experienced symptomatic UTI [hazard ratio 3.9; 95 % CI 1– 14; $P = 0.02$)	58.3% and 20.0% of UTI in the antibiotic and placebo groups, respectively were caused by SMZ + TMP-resistant bacteria ($P = 0.15$)
Märild, S	Prospective,	Febrile urinary tract	Orally administered ceftibuten	10 days	14% of *E. coli* isolates	Not reported

(2009)	coordinated, randomized, open, multicenter trial in UTI	infection (UTI) (N = 547 children aged 1 month to 12 years)	(9 mg/kg once daily; n = 368) and SMZ + TMP ((3 mg + 15 mg)/kg twice daily; n = 179)		resistant to SMZ + TMP; none to ceftibuten Bacteriological elimination rates at follow-up: ceftibuten, 91%; SMZ + TMP 95%, (95% CI) for difference of −9.7 to 1.0]. Clinical cure rate was significantly higher among ceftibuten group (93% vs 83%, 95% CI for difference of 2.4 to 17.0).	
Mathews R and Mattoo TK 2015	Review of the Randomized Intervention for Vesicoureteral Reflux (RIVUR) study (UTI) and 6 other studies from 2006–2010	Recurrent urinary tract infection (UTIs) in 100 children < 30 months of age with VUR with VUR in 6 studies including 100–243 children with age ranging from 0 to 12 years age and the RIVUR study including 607 children aged 2 to 72 months.	SMZ + TMP or placebo (Dose and route not reported)	Not reported	Statistically significant benefit using antibiotic prophylaxis in prevention of recurrent febrile/symptomatic UTI in children with VUR was demonstrated. This comparison confirmed the antibody prophylaxis efficacy observed in previous studies	Significant increase in the rate of SMZ + TMP-resistant *E. coli* UTIs in the prophylaxis versus the placebo group
Pennesi M (2008)	Randomized, open label in UTI	Pyelonephritis and Renal scars 100 children aged under 30 months with vesicoureteral reflux	SMZ + TMP: 1-2 mg/kg TMP, 5-10 mg/kg SMZ q.d. or no antibiotic prophylaxis	2 years	No difference in the risk for having at least 1 pyelonephritis episode between the	Not reported
		(VUR)	(Route not reported)		SMZ + TMP and control groups [relative risk (RR): 1.2 [95% CI: 0.68-2.11]. The presence of renal scars was similar with and without antibiotic prophylaxis [RR: 1.2 [95% CI: 0.68-2.11]	
The Randomized Intervention for Vesicoureteral Reflux (RIVUR) trial investigators (2014)	2-year, multisite, randomized, placebo-controlled trial in UTI	607 children aged 2-71 months with VUR and 1 or 2 febrile or symptomatic UTI/s	Oral TMP (3 mg/kg) and SMZ (15 mg/kg) q.d.* or placebo	Long-term prophylaxis	SMZ + TMP reduced the risk of recurrences by 50% (hazard ratio [HR], 0.50; 95% CI, 0.34 to 0.74) Renal scarring was not significantly between the prophylaxis and placebo groups (11.9% and 10.2%, respectively, *P*=0.55)	In 87 children with a first recurrence caused by *E coli*, resistance was 63% in SMZ + TMP group and 19% in the placebo group
Roussey-Kesler, G (2008)	Prospective randomized trial in UTI	Recurrent UTI in 255 children aged 1 month to 3 years with low grade VUR (grade I-III)	SMZ + TMP (2 mg/kg TMP and 10 mg/kg SMZ q.d.) or no treatment (Route not reported)	Long-term prophylaxis	No significant difference in the occurrence of UTI in the 2 groups (17% vs 26%, *P* = 0.2) SMZ + TMP significantly reduced UTI in boys (*P* = 0.013), particularly in boys with grade III	Not reported

					VUR (P =0.042)	
Infection Caused by a Wide Range of Organisms						
Brucellosis						
Roushan, MRH (2006)	Prospective cohort in Brucellosis	Brucellosis in 140 children aged ≤ 15 years	TMP 8 mg/kg. and SMZ 40 mg/kg per day b.i.d. (group 1) Rifampin 15 mg/kg per q.d. (group 2) (Route not reported)	6 weeks (Group 1) or 8 weeks (Group 2)	Cure rates were 89.1% (Group 1) and 95.5% (Group 2), respectively	Not reported
Hadadi A (2009)	Retrospective descriptive study of patients with brucellosis in Tehran/Iran	415 patients (age 12-80 years, including 20.5% below 20 years old, n = 85)	Rifampin and SMZ + TMP (n = 133); rifampin and doxycycline (n = 124); rifampin, SMZ + TMP, and gentamycine (n = 112); doxycycline, SMZ + TMP (n = 42); doxycycline, rifampin, SMZ + + TMP (n = 4) (Dose and route not reported)	At least 6 months of follow-up	All patients became symptom-free showing the initial response to the treatment; however, relapse was seen in 40 patients in the follow-up duration. The co-administration of doxycycline and SMZ + TMP led to low rate of relapse (2.5% CI: 0-12.5)	Not reported
Osteomyelitis						
Messina AF (2011)	Retrospective chart review SSTI	Acute osteomyelitis 20 children aged 9 months to 17 years	SMZ + TMP (median 16.4 mg/kg/d, divided every 6 to 12 h) Oral in 19 patients IV in 1 patient 15/20 patients received a vancomycin- or clindamycin-regimen for 1 to 26 days (median, 4.5 days) before changing therapy to SMZ + TMP	Median 40 days (range 26-59)	All 20 patients cured	Not reported
Toxoplasmosis						
Alavi SM (2010)	Randomized, double-blind, placebo-controlled study	Toxoplasmic lymphadenitis, n = 46 (mean age 13 years), including 32 patients < 15 years	48 mg/kg/day SMZ + TMP divided into two doses or placebo (route not reported)	1 month	A significantly greater proportion of patients with toxoplasmic lymphadenitis achieved a serological response and cure with SMZ + TMP compared with placebo (65% vs. 13%) Incidence of malaria was	Not reported
Unlabelled Indications						
Malaria						
Bigira, V (2014)	Randomized, controlled, open-label clinical trial	Malaria (400 infants were enrolled and 393 randomized at 6 months of age and chemoprevention was stopped at 24 months of age)	No chemoprevention or SMZ + TMP single dose q.d. or sulfadoxine-pyrimethamine single dose q.m.o. or dihydroartemisinin-piperaquine q.d. for 3 consecutive days per month	540 days	6.95 episodes/ person-years at risk (PYAR) in the no chemoprevention arm and 5.21 episodes PYARin the SMZ + TMP arm (Protective efficacy PE = 28% (95% CI, 7% to 44%)	24% had asymptomatic parasitemia at baseline
Davis, NL	Observational	Malaria	SMZ + TMP 240 mg q.d. . (n =	210 days	At least one episode of	P. falciparum 100%

(2015)	cohort study in Malaria	(882 infants aged from 6 to 36 weeks)	682)or or No treatment (n = 292) (Route not reported)		malaria was experienced in 114 [18%] infants in the SMZ + TMP arm and 67 [26%] infants in the no treatment arm.	
Fehintola, FA (2010)	Randomized clinical trial in Malaria	*Plasmodium falciparum* malaria (81 [57 completed] paediatric subjects, aged 0.5-12 y)	Artesunate (4 mg/kg bw in 2 divided doses daily for 3 days) plus either SMZ + TMP (20 mg/kg bw twice daily for 3 days) or chloroquine (10 mg/kg bw as single daily doses on Days 0 and 1, and 5 mg/kg bw on Day 2). All administered orally in tablet form.	3 days (14-day follow-up)	Fever clearance time (days): artesunate + SMZ + TMP (n = 31), 1.0 + 0; artesunate + chloroquine (n = 26), 1.14 + 0.38 ($P > 0.05$) Parasite clearance times (days): artesunate + SMZ + TMP, 1.65 + 0.49; artesunate + chloroquine, 1.58 + 0.67 Cure rates on Day 14 were 100% for both groups.	Not reported
Kapisi, JA (2015)	Randomized controlled trial In Malaria	Malaria (N = 393 [of 400 enrolled] infants 4-5 months old	Monthly sulfadoxine-pyrimethamine (SP), daily SMZ + TMP, or monthly dihydroartemisininpiperaquine (DP) (Dose and route not reported)	Study drugs administered through 24 months of age	At time of report, 277 were actively being followed and 78 had reached 24 months of age The incidence of malaria: no therapy = 5.69 episodes PPY; monthly SP = 5.47 episodes PPY (PE = 7%, 95% CI -17-26%); daily SMZ + TMP = 4.32 episodes PPY (PE = 26%, 95% CI 7-42%); monthly DP = 2.32 episodes PPY (PE = 60%, 95% CI 48-68%).	Not reported
HIV Exposed Children						
Kamya MR (2014)	Open-label, randomized controlled trial	200 HIV-exposed infants (biological mother with confirmed HIV-positive status) aged 4-5 months enrolled and 186 randomized after cessation of breastfeeding and confirmed to be HIV uninfected (median 10 months of age).	No chemoprevention or monthly sulfadoxine-pyrimethamine or daily SMZ + TMP or monthly dihydroartemisinin-piperaquine	From randomization to 24 months of age	The incidence of malaria in the no chemoprevention group was 6.28 episodes per person-year at risk. Protective efficacy was 69% (95% CI 53-80, P < 0.001) for dihydroartemisinin-piperaquine, 49% (95% CI 23-66, P = 0.001) for SMZ + TMP and 9% for sulfadoxine-pyrimethami	Not reported

					ne (95% CI −35 to 38, P = 0.65)	
Kinara, SO (2013)	Randomized controlled open-label study in Malaria	Malaria in HIV-exposed infants (N = 200 [186 randomized], aged 4-5 months)	Monthly sulfadoxine-pyrimethamine (SP), daily SMZ + TMP, or monthly dihydroartemisinin-piperaquine (DP). (Dose and route not reported)	Approximately 6 weeks after cessation of breastfeeding through 24 months of age	Incidence of malaria: No therapy group increased to 6.28 episodes PPY Monthly SP: PE of 9% (95% CI -35 to 38%, p = 0.65) Daily SMZ + TMP: PE of 49% (95% CI 23 to 66%, p = 0.001) Monthly DP: PE of 69% (95% CI 53 to 80%, p < 0.001).	
Mbeye, NM (2014)	Meta-analysis of 3 randomized controlled trials and 4 cohort studies in Malaria	Malaria (N=5039 children aged 6 weeks to 15 years: 1692 HIV-exposed; 2800 HIV-uninfected; 1486 HIV-infected)	SMZ + TMP (various doses depending on the studies, route not reported)		SMZ + TMP groups less likely to develop clinical malaria episodes than those without prophylaxis (combined IRR 0.37, 95% confidence interval: 0.21-0.66)	
Sandison, TG (2014)	Non-blinded randomized control trial in Malaria	SMZ + TMP prophylaxis for malaria in 203 breastfeeding HIV-exposed infants aged 6 weeks to 9 months in Uganda	SMZ + TMP syrup (40 mg TMP and 200 mg SMZ/5 mL suspension) was used in children < 15 kg: 2.5 mL/day for children = 4 kg in weight, 5	Prophylaxis for 2 years versus discontinuation immediately after breastfeeding cessation where no transfer of HIV had taken place	Malaria: 3.24 cases/person year of with 2-year prophylaxis versus 5.57 cases/person year in infants who stopped	No significant differences in the proportion of markers of antifolate resistance in
			mL/day for children > 4-8 kg, and 10 mL/day for children > 8-15 kg Children 10-15 kg were switched to SMZ + TMP tablets [80 mg TMP and 400 mg SMZ q.d.]		SMZ + TMP 39% reduction in malaria incidence adjusted for age at randomization (incidence rate ratio 0.61 [95% CI 0.46 to 0.81], *P* = 0.001).	malaria episodes in the two groups
HIV Infected Children						
Gasasira, AF (2010)	Comparison of subjects in 2 parallel cohort studies in Malaria	*Plasmodium falciparum* malaria in HIV infected children (292 of 809 subjects aged 1 to 10 years)	(SMZ + TMP) (Dose and route not reported)	29 months (median)	SMZ + TMP associated with protective efficacy of 80% (0.10 vs. 0.45 episodes per person year, p < 0.001); efficacy maintained over 3 consecutive 9.5-month periods (81%, 74%, 80% respectively, p = 0.506)	The prevalence of *dhfr* and *dhps* point mutations was evaluated in *P. falciparum* isolates. *Dhfr* 164L was found more frequently in HIV-infected treated children than in uninfected children
Homsy, J (2014a)	Randomized controlled open-label trial and 2 additional observational cohorts In Malaria	Malaria in HIV infected infants aged from 6 weeks until breastfeeding cessation (N = 203 (185 continued] from RTC; 48/148 from additional cohorts)	SMZ + TMP (Dose and route not reported)	Not reported	98/185 (52.97%) assigned to continue treatment to 2 y; at 2 y, 45/91 (49.45) continued to 4 y. 243 malaria episodes (2·91 per person-y) in the 45 infants assigned to continue SMZ + TMP until age 4 years	Not reported

					compared with 503 episodes (5·60 per person-y) in the 46 assigned to stop SMZ+TMP at age 2 years (incidence rate ratio 0·53, 95% CI 0·39-0·71; p<0·0001) 4-y SMZ+TMP associated with 47% lower risk of malaria than those ceasing after 2-y (IRR 0·53, 95% CI 0·39-0·71, p<0·0001)	
Homsy, J (2014b)	Randomized controlled open-label trial and 2 additional observational cohorts Malaria	Malaria in HIV infected infants up to 4 years of age (N=203 (185 continued] from RTC; 48/148 from additional cohorts)	SMZ+TMP (Dose and route not reported)	Not reported	152 (82.2%) and 148 (78.9%) followed to 4 and 5 years, respectively 43% reduction in malaria for those continuing SMZ+TMP to age 4 y (incidence rate ratio, 0.57; 95% CI, 0.49-0.66; p<0.001)	Not reported
Kasirye, R (2015)	Meta-analysis of 6 studies: 4 observational cohorts and 2 randomized	Malaria in HIV-positive individuals on antiretroviral therapy (ART) in 760 children with median age 7.9 or 899	SMZ+TMP and/or ART (Dose and route not reported)	Not reported	RCTs: Significant increase in smear-positive malaria on ART alone (IRR 32.5 CI=8.6-275.0 and HR	Not reported
	controlled trials In Malaria (including Bwakura-Dangarembiz et al (2014) and Gasasira et al (2010) described in this table)	children with median age 7.4 (HIV uninfected) or 5.7 (HIV infected)			2.2 CI=1.5-3.3) 2 OCS reported fewer parasitaemia episodes on SMZ+TMP and ART (OR 0.85 CI=0.65-1.11 and 3.6% vs 2.4% of samples P=0.14) One OCS found a 76% (95% CI=63-84%) vs 83% (95% CI = 74–89%) reduction in malaria incidence in children on SMZ+TMP and ART vs on SMZ+TMP only, when both were compared with HIV-negative children One OCS reported a 64% reduction in malaria incidence after adding ART to SMZ+TMP (RR=0.36, 95% CI=0.18-0.74)	
Skin and Soft tissue Infections (SSTI)						
Duong, M (2010)	Double-blind, randomized, controlled trial	*Staphylococcus aureus* and other infections (161 [149 completed] paediatric	Standard oral SMZ+TMP dose (10-12 mg TMP /kg/day divided into 2	10 days	Failure rate for placebo vs antibiotic groups was 4/76 (5.3%) vs 3/71	Not reported

	SSTI	subjects, 3 months-18 years)	doses, with a maximum dose of 160 mg TMP/dose; liquid formulation)		(4.1%) , respectively New lesions at 10-day follow-up: placebo, 19 (26.4%) vs antibiotic, 9 (12.9%); at 3-month follow-up: placebo, 15/52 (28.8%) vs antibiotic, 13/46 (28.3%)	
Hyun DY (2009)	Retrospective chart review SSTI	Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) in paediatric patients aged from 1 month to 17 years (median age of 10 months).	Oral SMZ + TMP (TMP TMP (mean 9.2 mg/kg/d ≤ 12 years old and 320 mg/d > 12 years old) (n = 215) or Oral clindamycin (mean 27.3 mg/kg/d ≤ 12 years old and 1470 mg/d > 12 years old; n = 200)	Mean 11.0 and 10.7 days with SMZ + TMP and clindamycin respectively	No significant difference between the 2 treatment in the percentage of returns to the hospital after discharge because of recurrence or worsening of the previous infection	CA-MRSA clindamycin resistance rate was 7.2%
Miller, LG (2015)	Multicenter, prospective, randomized, double-blind clinical trial SSTI	Uncomplicated skin infections: cellulitis, abscesses (524 patients, 29.6% children 6 to 11 months of age)	Clindamycin two 150-mg tablets t.i.d. or SMZ 800 mg and TMP 160 mg two single-strength tablets b.i.d.	10 days	In the population that could be evaluated (466 patients), the rate of cure was clindamycin: 89.5% (95% CI, 85.2 to 93.7) SMZ + TMP: 88.2% (95% CI, 83.7 to 92.7)	Not reported

Rapporteur´s comment: Lower respiratory tract infection

All three studies were performed in children 2-59 months of age covering both active substances. In the treatment of children with non-severe pneumonia, the authors concluded there was no difference in effectiveness between SMZ+TMP and oral amoxicillin. In the study by Rasmussen et al (2005), 1143 Pakistani children with childhood pneumonia were randomized to 4 mg TMP and 20 mg SMZ/kg (normal dose) or 8 mg TMP plus 40 mg SMZ/kg b.i.d (double dose) for 5 days. Treatment success was found to be similar in the standard dose and double dose groups. The study concluded that both standard and double strength SMZ+TMP were effective in treating non-severe pneumonia.

Lower respiratory tract infection in general is not an approved indication in all the countries, although pneumonia caused by Pneumocystis jiroveci is included in all the SmPCs. Non-severe lower respiratory tract infection can be considered supported by the studies submitted by this procedure, as SMZ+TMP was comparable to oral amoxicillin regarding efficacy and safety. However, there is not enough data to suggest the inclusion of lower respiratory tract infection as an indication in the SmPCs where it is not yet listed.

Regarding paediatric dosage regimens in general, the doses per kg body weight is stated in most SmPCs; eg. "t*he dosage for children is equivalent to approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kg body weight per day*". However, some of the SmPCs only contain the daily dosage according to the age of the child; eg. "*the schedules for children are according to the child's age and provided in the table below…*" (eg. the Latvian SmPC). As the weight among children of the same age might vary considerably, the Rapporteur believes the prescriber (and the patient) would benefit from the inclusion of weight-based doses in the SmPC. The MAH is asked to provide a discussion of the different ways to present the paediatric dosage, including benefits and drawbacks. The question is listed in the recommendation of this procedure.

In some SmPCs, it is recommended to increase the dose to one and a half the originally recommended one in the case of severe infection. In the study by Rasmussen et al (2005), the double dose was used in one of the arms, almost corresponding to one and a half of the commonly recommended dose. The effectiveness of the single and double doses for 5 days was found to be equal and no severe safety events were noted. Thus, the recommendation of

increasing the dose at severe infection is, based on the absence of severe AEs, supported by the study by Rasmussen et al. The MAH is asked to provide a discussion about efficacy and safety of increasing the dose of Bactrim in the case of severe infection. The discussion should list the clinical data available that support/do not support such an increase.

Rapporteur´s comment: Otitis media

The submitted studies were performed in children of the proper age, involving both active substances.

Soley et al (2007) conducted an open-label, double tympanocentesis, single-center study in 89 children (aged 3–48 months) with acute otitis media (AOM). The children received SMZ + TMP twice daily (40 mg/kg/d) for 10 days. Bacteriologic eradication was achieved in 80% of children (42 of 52 clinically and bacteriologically evaluable), and overall clinical response at the end of therapy was 78%. The authors concluded that SMZ+TMP clinical response was unsatisfactory, especially among culture-positive children. The Rapporteur finds it difficult to draw any conclusions based on these results, as the study was uncontrolled and the number of children included was not very large.

Rapporteur´s comment: Pneumocystis jiroveci pneumonia

Ten studies involving children and the two active substances in the prophylaxis of Pneumocystis jirovecii pneumonia were submitted.

Agrawal et al (2011) evaluated oral SMZ + TMP twice-weekly for *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis in 87 paediatric patients with acute lymphoblastic leukemia (ALL), using a retrospective chart review. Patients received SMZ + TMP (150/750mg/m2/day) divided b.i.d. on 2 consecutive days of the week, throughout the duration of chemotherapy and for 3-6 months afterwards. Among the 45 patients with positive chest X-rays, 24 had positive radiographs following anesthesia, 2 had pleural effusions, 1 had both post-operative changes and pleural effusions, and 18 had infiltrates and were initially treated for bacterial or fungal pneumonia. No cases of PJP were identified. The authors conclude that, while this is not a randomized controlled study, these findings suggest that twice weekly prophylactic regimen is a potential alternative for paediatric patients with ALL and in paediatric malignancies in general.

The dosage used in the study is within the recommendation. Based on the results, it might be an alternative to give the prophylaxis on 2 consecutive days of the week rather than 3 consecutive days as recommended in most SmPCs. However, more study results are needed in order to make such an update of the recommendations.

Caselli et al (2014) compared once-weekly, twice-weekly, and three times weekly oral SMZ + TMP dosing regimens for PJP prophylaxis in 2466 paediatric patients with newly-diagnosed cancer requiring chemotherapy over a 3-year period (2009–2011). Two cases of PJP (0.08% of patients) were reported, both in the 2-day/week prophylaxis group. Subsequent investigation revealed that neither patient was receiving prophylaxis at the time of the event. Cumulative incidence of PJP was very low with each treatment regimen, indicating that a single-day course of SMZ + TMP prophlyaxis may be sufficient in preventing PJP in children with cancer undergoing intensive chemotherapy, with the potential for improved adherence to therapy given the simplified regimen compared with twice- or three times-weekly schedules.

This study supports the results from the study by Agrawal et al, discussed above, regarding the administration of th prophylaxis less than three times weekly as recommended today.

The results regarding the optimal frequency for giving prophylactic SMZ+TMP are not conclusive, although the populations among the studies vary regarding underlying diseases. More studies with conclusive results are needed in order for the SmPC text to be updated regarding the frequency of prophylactic administration.

The results from the submitted studies regarding PJP support the present indications in the SmPC and the Rapporteur agrees with the MAH that no changes are currently warranted.

Many of the SmPCs could preferably be updated regarding the wording *carinii* to *jirovecii*. The MAH is asked to comment on this suggestion.

Rapporteur´s comment: Urinary tract infection

Eight studies were submitted involving children (over the entire approved age range) and SMZ+TMP in the treatment/prophylaxis of urinary tract infection (UTI). This is currently an approved indication only in some of the national SmPCs (eg. Estonia, France, Italy, Portugal and Sweden).

The submitted studies did show varying results for the treatment/prophylaxis of UTI with SMZ+TMP. Some of the studies showed a modest or significant decrease of UTI recurrence among predisposed children when using long term SMZ+TMP. Others indicated that longterm prophylaxis with SMZ+TMP was associated with an increased risk of symptomatic UTI compared to placebo in children with vesico-urethral reflux. Renal scarring did not differ significantly between the prophylaxis and placebo groups.

In one study, SMZ+TMP was compared with ceftibuten in paediatric patients with febrile UTI (Mårild et al, 2009). The authors saw that the clinical cure rate was significantly higher among the ceftibuten group than the SMZ+TMP group. The increasing resistance rates against SMZ+TMP (especially in certain regions) may contribute to make SMZ+TMP a not so useful alternative for the empirical treatment of febrile UTI in children. In conclusion, due to the large national variations in drug resistance pattern, the Rapporteur would like to emphasize the importance of following the national guidelines on the use and prescription of antibiotics.

There is not enough new significant information leading to proposed modifications of the SmPC from this review of data.

Rapporteur´s comment: Infection caused by a wide range of organisms

Results from two studies regarding brucellosis were submitted. One of them involved children and the other one both children and adults. Other studies submitted involving children of the proper age and the two active substances dealt with osteomyelitis (1 study) and toxoplasmosis (1 study).

Going through these studies led to the Rapporteur conclusion that the clinical benefit of Bactrim therapy is in line with current labelling.

Rapporteur´s comment: other use

Malaria

Results from four studies regarding the use of SMZ+TMP for prevention/treatment of malaria were submitted. These studies were conducted in children and involved both active substances.

The results were not entirely conclusive. Some studies indicated that SMZ+TMP reduced overall malaria infections fairly well, whereas other studies showed that dihydroartemisinin-piperaquine (DP) had a clearly superior protective efficacy compared to SMZ+TMP. In one study, it was concluded that artesunate plus SMZ+TMP had similar efficacy as artesunate plus chloroquine in the treatment of acute uncomplicated Plasmodium falciparum malaria in children resident in an endemic area of Southwest Nigeria. The data on this topic is still to sparse to draw any firm conclusions. No modification of the SmPC is warranted based on this data.

Malaria in HIV-exposed children

Four studies on this topic were submitted. All of the studies involved children and the two active substances. Most of the studies showed a protective effect of SMZ+TMP against malaria in HIV-exposed children.

Malaria in HIV-infected children

Regarding the preventing effect of SMZ+TMP against malaria in HIV-infected children, four studies were submitted. All of them involved children and SMZ+TMP.

It was concluded in the studies that daily treatment with SMZ+TMP was effective in protecting children with HIV infection against malaria. However, it was shown that certain point mutations was associated with the use of SMZ+TMP; eg. *dhfr* 164L was found more frequently in HIV-infected treated children (8%) than in uninfected children (1%; *p*=0.001) who did not receive SMZ+TMP.

Skin and soft tissue infections

Three relevant studies were submitted. The results showed that SMZ+TMP and clindamycin may be equivalent as outpatient oral therapies for skin and soft tissue infections. In some SmPC, clinically relevant spectrum of activity is specified, including skin and soft tissue bacteria including Staphylococcus. The results from these studies support this statement. No changes of the SmPC is warranted.

Rapporteur´s overall comment on the literature

The majority of the studies are performed in children of the proper age involving both active substances with doses within the recommended range.

Regarding paediatric dosage regimens, the doses per kg body weight is stated in most SmPCs; eg. "t*he dosage for children is equivalent to approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kg body weight per day*". However, some of the SmPCs only contain the daily dosage according to the age of the child; eg. "*the schedules for children are according to the child's age and provided in the table below…*" (eg. the Latvian SmPC). As the weight among children of the same age might vary considerably, the Rapporteur believes the prescriber (and the patient) would benefit from the inclusion of weight-based doses in the SmPC. The MAH is asked to provide a discussion of the different ways to present the paediatric dosage, including benefits and drawbacks. The question is listed in section VI.

In some SmPCs, it is recommended to increase the dose to one and a half the originally recommended one in the case of severe infection. In the study by Rasmussen et al (2005), the

double dose was used in one of the arms, almost corresponding to one and a half of the commonly recommended dose. The effectiveness of the single and double doses for 5 days was found to be equal and no severe safety events were noted. Thus, the recommendation of increasing the dose at severe infection is, based on the absence of severe AEs, supported by the study by Rasmussen et al. The MAH is asked to provide a discussion about efficacy and safety of increasing the dose of Bactrim in the case of severe infection. The discussion should list the clinical data available that support/do not support such an increased dose.

Many of the SmPCs could preferably be updated regarding the wording Pneumocystis *carinii* to *jirovecii*. The MAH is asked to comment on this suggestion.

5. Drug resistance

Significant intra- and inter-country differences in SMZ + TMP resistance have been reported in the literature. A comprehensive literature search has been performed to identify emerging information on the SMZ + TMP resistance in the treatment and prophylaxis of infection.

High prevalence and regional difference of SMZ + TMP resistance are believed to be due to previous antibiotic use, particularly in HIV-positive patients administered SMZ + TMP as prophylaxis against PJP [Lalitha et al. 2013, Gupta et al. 2011, Chow et al. 2012], but may in part also reflect changes in Clinical and Laboratory Standards Institute and The European Committee on Anti-Microbial Susceptibility Testing susceptibility breakpoints in 2010/2011.

When SMZ + TMP is used, it is essential to know the resistance profile of the causative bacterial pathogen or to be very well aware of the local resistance situation for the major bacterial pathogens [Huovinen et al 2001]. This stresses the importance of performing qualified susceptibility testing and providing regular, timely bacterial susceptibility reports to clinicians in both hospital and community settings. The usefulness of SMZ + TMP can only be justified after careful local consideration of the resistance situation [Huovinen et al 2001].

Rapporteur's comment:

The Rapporteur agrees with the MAH that it is important to be aware of the large national/regional variations in SMZ+TMP resistance in order to choose a proper antibiotic. Before prescribing an antibiotic, including Bactrim, national/local guidelines on the use of antibiotics should always be considered.

6. Safety results

Since initial market approval in Austria on 1 April 1969, and until the end of the reporting period for the latest PBRER (1063730, 31 March 2015), Bactrim [sulfamethoxazole (SMZ)/ trimethoprim (TMP)] has been approved for use in approximately 100 countries worldwide.
In paediatric patients (≤18 years, i.e., including children and adolescents), the estimated cumulative exposure to Bactrim in Roche-sponsored interventional trials is 427 patients and the total estimated cumulative market exposure via commercially obtained drug (Roche data only, excl. external partners) to 31 March 2015 is 825,026,525 patients.

- Safety topics in paediatric patients from previous PSURs

No new significant safety information regarding the use of SMZ + TMP in paediatric patient population was observed during the reporting periods of the two most recent EU Periodic Safety Update Reports (PSUR). A summary of these PSURs is provided in the table below.

PSUR No	Reporting Period	Observations and conclusions as related to the paediatric exposure
Summary Bridging Report (SBR; 1031846) covering three PSURs	1 April 2006 to 01 April 2009	No new significant safety information regarding the use of SMZ + TMP in this patient group that included 27 neonates/infants and 133 children/adolescents.
Summary Bridging Report (SBR; 1047636) covering three PSURs	01 April 2009 to 31 March 2012	No new significant safety information regarding the use of SMZ + TMP in this patient group that included 26 neonates/infants and 111 children/adolescents.

- Published literature

Among the published literature reviewed from 1 January 2005 to 31 March 2015 as part of the periodic signal detection and evaluation for SMZ + TMP, a large retrospective observational study conducted between 1 January 2000 and 31 December 2009 to characterize the adverse drug reactions (ADR) profile of SMZ + TMP in children was identified as worth for discussion (Goldman et al 2013).

In this study, 109 children were diagnosed with a SMZ + TMP ADR based on medical chart review (5 cases from 2000 to 2004 as compared with 104 cases from 2005 to 2009). Fifty-eight percent (63/109) had been treated for a skin and soft tissue infection and 21% (23/109) for urinary tract infection. A similar trend was observed nationally, where the incidence of SMZ + TMP ADRs more than doubled from 2004 to 2009 at comparable paediatric hospitals. Although national outpatient data revealed no change in overall SMZ + TMP prescribing, the percentage of children prescribed SMZ + TMP for skin and soft tissue infection sharply increased during the study period (0%–2% [2000-2004]; 9%–17% [2005–2009]). Of the patients with SMZ + TMP ADRs, 37% (40/109) were hospitalized. Hospitalized patients more frequently had mucous membrane involvement, documented fever, vomiting, or diarrhoea as compared with patients evaluated in the Emergency Department.

Authors concluded that the increase in TMP + SMX ADRs rate from 2000 to 2009 could be explained by the significant increase in TMP + SMX prescribing for methicillin-resistant Staphylococcus aureus (MRSA) infections approximating that time period in the USA. This prescribing pattern may have resulted in a continued increase of drug-associated ADRs. Authors also acknowledged that this study was limited because the chart review was retrospective in nature and the diagnosis of a SMZ + TMP ADR was determined by the clinician without any specific inclusion criteria. Moreover, the clinical information recorded in the charts varied by case, and detailed information on SMZ + TMP dose, route of administration, and duration of exposure were not regularly recorded. Lastly, additional cases could have been overlooked if not coded properly.

Rapporteur´s comment

The Rapporteur agrees with the MAH that it is not unexpected that certain events were more frequently detected in hospitalized children since they might represent children with underlying severe conditions who need observation and medical care in a hospital setting. All ADRs reported in the study discussed above are already labelled ADRs for Bactrim. Moreover, only a slight increase in the rate of events reported in paediatric patients into the Roche global safety database regarding SMZ+TMP was observed over the period from 1 January 2005 to 31 December 2009, as compared to the previous 5-year interval (14 versus 12 %).

- Evidence from the company safety database

The Roche global safety database was searched for all events reported with SMZ + TMP from 1 January 2005 to 31 March 2015 in the paediatric population (QTT040381). The cut-off date of 31 March 2015 was chosen for consistency with the cut-off date of the last annual PBRER submitted to non-EU countries. Data have been reviewed for two age-groups separately: children (aged 0 to 12 years) and adolescents (>12 years to 18 years). This approach has been taken since dosage recommendations for Bactrim differ between these two groups. Dosage in children up to 12 years is calculated to achieve an equivalent to a dose of 6 mg TMP and 30 mg SMZ per kg bodyweight per 24 hours whereas the standard adult dosage is recommended for children over 12 years (i.e., adolescents).

During the 10-year interval, 1,557 events were reported in 758 cases in the children group (of which 293 with at least one serious event): 370 female subjects and 368 male subjects (in 20 cases gender was not reported).

The most commonly affected SOCs and the most common adverse events within these SOCs are in line with the labelled ADRs listed in the Bactrim CDS or with symptoms commonly observed in this patient population or with Bactrim indications.

SOC	Adverse events
Infections and infestations	Ear infections Pneumocystis jirovecii pneumonia Pneumonia
Blood and lymphatic system disorders	Agranulocytosis[1] Anemia[1] Neutropenia[1] Thrombocytopenia[1] Pancytopenia[1]
Immune system disorders	Hypersensitivity[1]
Metabolism and nutrition disorders	Decreased appetite
Psychiatric disorders	Hallucination[1]
Nervous system disorders	Headache
Eye disorders	Eye pruritus Eye swelling Eyelid edema Ocular hyperemia
Respiratory, thoracic and mediastinal disorders	Cough[1]
Gastrointestinal disorders	Vomiting[1] Diarrhoea[1] Abdominal pain

	Nausea[1]
Skin and subcutaneous tissue disorders	Rash[2] Erythema[2] Pruritus[2] Urticaria[2] Stevens-Johnson syndrome[1]
General disorders and administration site conditions	Pyrexia[1]

1. Labelled ADR in Bactrim CDS; 2. Labelled in Bactrim CDS as multiple skin reactions.

During the 10-year interval, 561 events were reported in 237 cases in the adolescent group (of which 131 with at least one serious event): 133 female subjects and 104 male subjects.

The most commonly affected SOCs and the most common adverse events within these SOCs are in line with the labelled ADRs listed in the Bactrim CDS or with symptoms commonly observed in this patient population.

SOC	**Adverse events**
Blood and lymphatic system disorders	Thrombocytopenia[1] Neutropenia[1] Leukopenia[1] Agranulocytosis[1]
Immune system disorders	Hypersensitivity[1]
Nervous system disorders	Headache
Respiratory, thoracic and mediastinal disorders	Cough[1] Dyspnea
Gastrointestinal disorders	Vomiting[1] Nausea[1] Abdominal pain
Hepatobiliary disorders	Hepatocellular injury[1]
Skin and subcutaneous tissue disorders	Rash[2] Pruritus[2] Urticaria[2] Erythema[2] Stevens-Johnson syndrome[1]
General disorders and administration site conditions	Pyrexia[1]

1. Labelled ADR in Bactrim CDS; 2. Labelled in Bactrim CDS as multiple skin reactions.

No significant pattern of concern regarding latency, outcome and actions taken was observed between these two groups or as compared to the adults group.

Thirteen overdose cases in paediatric patients (11 in children and 2 in adolescents) were reported over the 10-year interval of which 5 were not associated with any adverse events and 8 with adverse events labelled as ADR in Bactrim CDS. Resolution of adverse events was reported in 7 of these 8 cases and 1 had a fatal outcome (AER1086605-2) due to acute renal failure related to overdose of vancomycine and voriconazole in a 15-year old female patient with pulmonary aspergillosis and idiopathic bone marrow aplasia.

Rapporteur´comment

The Rapporteur´s conclusion is that no new significant safety information raising suspicions of new safety signals pertinent to the paediatric patient population was observed during the periodic signal detection and evaluation for SMZ + TMP over a 10-year period.

Rapporteur´s overall comment on the data submitted by Roche

The MAH considers that no changes to the currently approved SmPCs are warranted. However, after going through the submitted data (eg. MAH sponsored studies, literature and safety data) the Rapporteur has a few suggestions and questions regarding the SmPC wording, mainly in section 4.1. These suggestions/questions are listed in section VI.

The wording of some of the current SmPCs regarding the paediatric population is not in agreement with the Guideline on Summary of Product Characteristics (September 2009) and should therefore be updated with information on age groups in section 4.1:

X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.

Regarding paediatric dosage regimens, the doses per kg body weight is stated in most SmPCs; eg. "t*he dosage for children is equivalent to approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kg body weight per day*". However, some of the SmPCs only contain the daily dosage according to the age of the child; eg. "*the schedules for children are according to the child's age and provided in the table below…*" (eg. the Latvian SmPC). As the weight among children of the same age might vary considerably, the Rapporteur believes the prescriber (and the patient) would benefit from the inclusion of weight-based doses in the SmPC. The MAH is asked to provide a discussion of the different ways to present the paediatric dosage, including benefits and drawbacks of each way. The question is listed in section VI.

In some SmPCs, it is recommended to increase the dose to one and a half the originally recommended one in the case of severe infection. In the publication by Rasmussen et al (2005), the double dose was used in one of the arms, almost corresponding to one and a half of the commonly recommended dose. The effectiveness of the single and double doses for 5 days was found to be equal and no severe safety events were noted. Thus, the recommendation of increasing the dose at severe infection is, based on the absence of severe AEs, supported by the study by Rasmussen et al. The MAH is asked to provide a discussion about efficacy and safety of increasing the dose of Bactrim in the case of severe infection. The discussion should list the clinical data available that support/do not support such an increased dose.

Many of the SmPCs could preferably be updated regarding the wording Pneumocystis *carinii* to *jirovecii*. The MAH is asked to comment on this suggestion.

Except the comments mentioned above, the data submitted by the MAH does not warrant any major changes of the paediatric sections of the SmPCs and does not give rise to any new safety concerns except those already known and labelled for. The Rapporteur agrees with the MAH that it is important to be aware of the large national/regional variations in SMZ+TMP resistance in order to choose a proper antibiotic. Before prescribing an antibiotic, including Bactrim, national/local guidelines on the use of antibiotics should always be considered.

Polfa

1. Introduction

Biseptol 480 is indicated for the treatment of the following infections when owing to sensitive microorganism (see section 5.1):

- Acute uncomplicated urinary tract infection.

It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than a combination such as co-trimoxazole for infusion

- Treatment and prevention of *Pneumocystis jiroveci* pneumonitis
- Treatment and prophylaxis of toxoplasmosis.

- Treatment of nocardiosis

In general, the indications for the use of co-trimoxazole for infusion are the same as those for oral presentations.

Standard dosage recommendations for acute infections:

Adults and children over 12 years
2 ampoules (10 ml) every 12 hours.

Children aged 12 years and under
The recommended dosage is approximately 30 mg sulfamethoxazole and 6 mg trimethoprim per kg bodyweight per 24 hours given in two equally divided doses. As a guide the following schedules may be used; before use Biseptol 480 should be diluted as described in section 6.6.

Children from 6 weeks to 5 months: 1.25 ml every 12 hours.
Children from 6 months to 5 years: 2.5 ml every 12 hours.
Children from 6 to 12 years: 5 ml every 12 hours.

For severe infection, dosage may be increased by 50% in all age groups.

Treatment should be continued until the patient has been symptom free for two days; the majority will require treatment for at least 5 days.

2. Clinical studies

➢ Methods

The MAH submitted one research report performed in Poland in 1989. The report involves Biseptol 480 for intravenous use in children. The purpose of the study was:

- Assessment of the effectiveness of treatment in bacterial infections in children,
- Assessment of the sensitivity of the bacterial strains before Biseptol administration,
- Assessment of the adverse effects of the drug on the basis of clinical observations and laboratory investigations.

The study was carried out on 50 children aged from 1 month to 16 years. The children were divided into two groups:

- Group I of 33 children receiving Biseptol therapeutically,
- Group II of 17 children receiving Biseptol prophylactically.

The indications for intravenous treatment with Biseptol in group I was in most cases infections with bacteria of in vitro documented sensitivity to both Biseptol components. The indications for prophylactic use of Biseptol included bladder catheterization and implantation of Tenckhoff catheter for continuous ambulatory peritoneal dialysis.

- **Results/conclusions**

The conclusions from the study were:

- Biseptol for i.v. use was found to be a valuable drug in children, particularly
  - In cases of poor tolerance of the oral form of Biseptol
  - In cases of inaccessibility of the oral route
  - In cases in which a high blood drug level must be rapidly achieved
- A high proportion of isolated bacterial strains were in vitro sensitive to Biseptol. The clinical effectiveness of the drug was usually in agreement with in vitro sensitivity of the pathogen
- Using in cases of renal failure, a favourable therapeutic effect was obtained when doses adjusted to the degree of renal failure were used, and no adverse effects of the drug was noted
- Biseptol for i.v. use given in a single dose was effective in prevention of infections during urological diagnostic and therapeutic procedures
- No adverse clinical or laboratory side effects previously described were observed

Rapporteur´s overall comment on the data submitted by Polfa

The MAH submitted a single research report, performed in Poland many years ago (eg. 1989). As the report is rather old, it is difficult to apply the conclusions on the current situation. In particular, the antibiotics resistance situation is expected to be very different today, and the isolates proven to be sensitive to Biseptol in 1989 do not necessarily present the same pattern today. Therefore, the clinical effectiveness of Biseptol in 1989 cannot automatically be considered to be the same today.

The same comment as given to Roche is valid for Polfa; eg. the wording of some of the current SmPCs regarding the paediatric population is not in agreement with the Guideline on Summary of Product Characteristics (September 2009) and should therefore be updated with information on age groups in section 4.1:

X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>.

Based on the submitted study report, no new significant information leading to any other proposed modifications of the SmPC has been identified by the Rapporteur. No statement by the MAH has been given regarding its opinion of the potential need for any SmPC update during this procedure.

Discussion on clinical aspects and conclusion

Two MAHs submitted a large number of completed paediatric studies for sulfamethoxazole + trimethoprim, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

One of the MAHs stated initially that the submitted paediatric studies do not influence the benefit risk for their products and that there is no consequential regulatory action. The other MAH did not submit a cover letter or an overview and did not give any statement of their opinion regarding the need of any SmPC update based on the submitted data.

Both MAHs should state in which age groups the product is indicated specifying the age limits, e.g. *'X is indicated I <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>>,* in the SmPC section 4.1. The MAHs should also update the PIL in accordance with the revisions in the SmPC, when relevant.

The studies related to MAHs specific products are discussed under each MAH:

Bactrim (Roche)
No changes in the currently approved SmPC for Bactrim were proposed by the MAH.

The MAH submitted 12 reports (10 on efficacy and safety; 2 on pharmacokinetics) of paediatric MAH sponsored studies involving Bactrim administered to children. Moreover, 54 literature references and a large amount of safety data was reviewed and submitted. In general, the submitted data do not give any reason to change the current recommendations regarding the use of this product in children. A few proposals/questions regarding potential SmPC modifications have been identified by the Rapporteur. The raised issues relates to paediatric dosage regime, increase of the dose to one and a half the originally recommended one in the case of a severe infection, update of the wording *Pneumocystis carinii to Pneumocystis jiroveci* (see section V). The safety data presented do not give rise to any new concerns in the paediatric population.

SmPC modifications are proposed for section 4.1 and 4.2 in some SmPCs. Refer to the section VI below.

Biseptol (Polfa)
The MAH submitted a single research report from the year of 1989. Based on the submitted study report, no new significant information leading to any other proposed modifications of the SmPC has been identified by the Rapporteur. No statement by the MAH has been given regarding its opinion of the potential need for any SmPC update during this procedure.

SmPC modifications are proposed for section 4.1 in some SmPCs. Refer to the section VI below.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Two MAHs submitted completed paediatric studies for sulfamethoxazole + trimethoprim. Roche submitted a large number of reports and Polfa only a single report.

Roche stated initially that the submitted paediatric studies do not influence the benefit risk for their products and that there is no consequential regulatory action. Polfa did not provide any statement at all. Nevertheless, during the procedure a proposal to modify the SmPCs of both MAHs has been made by the Rapporteur. See recommendation below.

- **Recommendation**

Type IB/II variations as appropriate to be requested from the MAHs within 90 days of publication of this public assessment report.
The PI for products with these substances should be updated with missing information in all sections of the PI as appropriate (and data if needed). Other sections *may* be affected (e.g. section 4.4 where changes may be required depending upon changes in section 4.3).

The following SmPC modifications are recommended:

Section 4.1

- It should be stated in which age groups the product is indicated, specifying the age limits, e.g. ***X is indicated in <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>***

- "***Consideration should be given to official guidance on the appropriate use of antibacterial agents***" should be added

Section 4.2

- Regarding paediatric dosage regimens, both dosing options; eg. based on weight and age respectively, should be included in the SmPC.
  -Doses per kg body weight: "***the dosage for children is equivalent to approximately 6 mg trimethoprim and 30 mg sulfamethoxazole per kg body weight per day***".
  -Daily dosage according to age: "***the schedules for children are according to the child's age and provided in the table below…***".

- The contraindication for treatment with SMZ+TMP should be children <6 weeks of age. Children >6 weeks should be included in section

- The SmPC should be updated regarding the wording ***Pneumocystis carinii*** to ***Pneumocystis jirovecii***.

Sections 4.3

"***Co-Trimoxazole should not be given to infants during the first 6 weeks of life***".

Section 5.2

- The following text should be added:

"***The pharmacokinetics in the pediatric population with normal renal function of both components of <Product >, TMP and SMZ are age dependent. Elimination of TMP-SMZ is reduced in neonates, during the first two months of life, thereafter both TMP and SMZ show a higher elimination with a higher body clearance and a shorter elimination half-life. The differences are most prominent in young infants (> 1.7 months up to 24 months) and decrease with increasing age, as compared to young children (1 year up to 3.6 years), children (7.5 years and < 10 years) and adults (see section 4.2)***"

The following PL modifications are proposed:

Section 1

- It should be stated in which age groups the product is indicated, specifying the age limits, e.g. ***X is used for <adults><neonates><infants><children> <adolescents> <aged x to y <years, months>***

The age specification should be stated as a concluding statement after any details about indicated infections.

Section 2

- The following information should be added:

  "***Co-Trimoxazole should not be given to infants during the first 6 weeks of life***".

Section 3

- Regarding paediatric dosage regimens, both dosing options; eg. based on weight and age respectively, should be included in the PL.
  -Daily dosage according to age *and* doses per kg body weight: "***the schedules for children are according to the child's age and body weight provided in the table below…***".

Carefully describe age intervals to avoid any gaps (e.g. 1-2 years and 3-4 years where it may be confusing whether it means 12-24 months and 36-48 months – where will children aged 25-35 months be included?)

- The PL should be updated regarding any wording of ***Pneumocystis carinii*** to ***Pneumocystis jirovecii***.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Name of medicinal product	**Pharmaceutical form**	**Strength**	**MAH**
Biseptol	Concentrate for solution for infusion	80mg/ml+16mg/ml	Polfa Warszawa S.A.
Bactrim	Oral solution (syrup); Tablets; Forte tablets; Intravenous infusion;	40mg/ml+8mg/ml 400mg/80mg 800mg/160mg 80mg/ml+/16mg/ml	Roche Registration Ltd., U.K.