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

Doxycycline
Vibramycin

UK/W/0090/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	12th December 2017

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	See Section VI
INN (or common name) of the active substance(s):	Doxycycline
MAH:	See Section VI
Pharmaco-therapeutic group (ATC Code):	Antibacterials for systemic use: Tetracyclines J01AA02
Pharmaceutical form(s) and strength(s):	Capsules containing 50, 100 or 200 mg of doxycycline as the hyclate salt Film-coated tablets containing 50 or 100 mg of doxycycline as the hyclate salt Dispersible tablets containing 100 mg of doxycycline as the monohydrate salt Syrup containing 10 mg/mL doxycycline as the hyclate salt Syrup containing 10 mg/mL of doxycycline as the calcium salt Oral suspension containing 25 mg/5 mL of doxycycline as the monohydrate salt Doxycycline Hyclate Solution 100 mg/5 mL is a sterile solution for injection.

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 4.1, 4.2, 4.3, 4.4 and 4.8.

Summary of outcome

☐ No change

☒ Change

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

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

☒ Paediatric information clarified: sections 4.1, 4.2, 4.3, 4.4 and 4.8.

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

II. RECOMMENDATION

Based on the data provided as part of this European paediatric work-sharing procedure with Article 45 of the Regulation (EC) No 1901/2006 as amended, on medicinal products for paediatric use, the benefit: risk balance of doxycycline has changed for the paediatric population.

The submitted data support the lifting of the contraindication in children aged younger than 12 years and replacement with a warning in children younger than the age of 8 years. Furthermore, the data are insufficient to recommend any new indications for doxycycline use.

Proposed changes to Sections 4.1, 4.2, 4.3, 4.4 and 4.8 of the Vibramycin SmPC and the PIL are detailed in **Section V.** The proposed modifications for the Vibramycin SmpC and the PIL are applicable to all similar products with a license for use in children. For member states with unrestricted doxycycline use in children aged 8 years to 12 years, the proposed precautionary statement for this age group will not be a mandatory requirement for this Article 45 work-sharing procedure. Furthermore, the exact text of the precautionary wording should be adapted to the approved indications of the respective products in individual member states.

These changes to should be submitted to national competent authorities for review via a variation procedure.

III. INTRODUCTION

The MAH submitted 72 completed paediatric studies (20 MAH-sponsored and 52 from a literature review) for Doxycycline in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended, on medicinal products for paediatric use.

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline and is available as doxycycline monohydrate and doxycycline hyclate (hydrochloride hemiethanolate hemihydrate). It has antimicrobial activity against a broad range of aerobic and anaerobic gram-

positive and gram-negative pathogenic bacteria including chlamydiae, mycoplasmas, rickettsiae, and some protozoa. It is indicated for prophylaxis and for the treatment of infections caused by the above-mentioned microorganisms.

Doxycycline received the first regulatory approval on 05 May 1967 in the UK. It is approved in 122 countries worldwide and is currently marketed in 66 countries.

A short critical expert overview has also been provided.

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

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

- A line listing

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

In the UK, the licensed paediatric indications for doxycycline (in children 12 to 17 years) are:

Treatment of a variety of infections caused by susceptible strains of Gram-positive and Gram-negative bacteria and certain other micro-organisms.

- Respiratory tract infections: Pneumonia and other lower respiratory tract infections due to susceptible strains of *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae* and other organisms. *Mycoplasma pneumoniae*. Treatment of chronic bronchitis, sinusitis.
- Urinary tract infections: Caused by susceptible strains of *Klebsiella* species, *Enterobacter* species, *Escherichia coli, Streptococcus faecalis* and other organisms.
- Sexually transmitted diseases: Infections due to *Chlamydia trachomatis* including uncomplicated urethral, endocervical or rectal infections. Non-gonococcal urethritis caused by *Ureaplasma urealyticum* (T-mycoplasma). It is also indicated in chancroid, granuloma inguinale and lymphogranuloma venereum. Vibramycin is an alternative drug in the treatment of gonorrhoea and syphilis.
- Skin infections: Acne vulgaris, when antibiotic therapy is considered necessary.

Vibramycin is a member of the tetracycline series of antibiotics, thus it may be expected to be useful in the treatment of infections such as:

- Ophthalmic infections Due to susceptible strains of gonococci, staphylococci *and Haemophilus influenzae*. Trachoma is not always eliminated.
- Rickettsial infections: Rocky Mountain spotted fever, typhus group, Q fever, *Coxiella* endocarditis and tick fevers.
- Other infections: Psittacosis, brucellosis (in combination with streptomycin), cholera, bubonic plague, louse and tick-borne relapsing fever, tularaemia, glanders, melioidosis, chloroquine-resistant falciparum malaria and acute intestinal amoebiasis (as an adjunct to amoebicides).

Vibramycin is an alternative drug in the treatment of leptospirosis, gas gangrene and tetanus.

- Prophylaxis in the following conditions: Scrub typhus, travellers' diarrhoea (enterotoxigenic *Escherichia coli*), leptospirosis and malaria. Prophylaxis of malaria should be used in accordance to current guidelines.

In addition to those listed above, the British National Formulary for children (BNF-C) includes recommendation for use for periodontitis and the treatment and post exposure prophylaxis for anthrax. It should be noted these are both unlicensed indications in paediatrics in the UK.

In the UK, there is a class contraindication for the tetracyclines in children younger than 12 years due to the risk of deposition in growing bone and teeth, by binding to calcium, which results in staining and occasionally dental hypoplasia. Despite this contraindication in the UK, paediatric dosing is available in the BNF-C for the treatment of anthrax in children aged 1 month to 17years.

In other EU member states (MSs), a similar contraindication for the tetracycline class exists, but in children younger than 8 years. A few EU MSs have only a warning about this class effect in Section 4.4 of the SmPC.

In the US, in addition to the indications listed above, doxycycline is also licensed for anthrax caused by *Bacillus anthracis*, including inhalational anthrax (post exposure) to reduce the incidence or progression of the disease following exposure to aerosolised *B. anthracis*.

The US label for doxycycline has only a warning for use in paediatrics. This states that "*the use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-grey-brown). This adverse reaction is more common during long-term use of the drugs, but it has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Use doxycycline in paediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g., anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies.*" Posology is available in the US label for children younger than 8 years old.

Doxycycline oral dosage and parenteral formulations were developed in the 1960s and are commercialised globally. Doxycycline is available in several pharmaceutical dosage forms which were used in the submitted studies.

Table 1: Doxycycline Dosage Forms

Dosage Form	Active Ingredient	Additional Detail
Capsule	Doxycycline Hyclate	
	Doxycycline Monohydrate	
Tablet	Doxycycline Hyclate[a]	Film-coated
	Doxycycline Hydrochoride	
	Doxycycline Monohydrate	Dispersible (orodispersable)
	Doxycycline Monohydrate	Non-dispersible
Syrup	Doxycycline Hyclate	Also referred to as Doxycycline Calcium Syrup
	Doxycycline Monohydrate	

Dosage Form	Active Ingredient	Additional Detail
Solution for Injection	Doxycycline Hyclate	Solution for injection

a. Doxycycline hyclate and doxycycline hydrochloride are chemically same and only differ in nomenclature.

Rapporteur's comments:

Doxycycline has several specific paediatric formulations authorised in EU and UK; however not all the paediatric formulations are readily available due to the inconsistencies in age range for the contraindication in children. It is observed that older antibiotics of the tetracycline class have contraindication in children less than 12 years in the UK or less than 8 years in other EU member states. A newer tetracycline derivative, tigecycline, was licensed in children via an EU centralised procedure in April 2015 (EMA/CHMP/262234/2015) and has only a warning for use under the age of 8 years because of tooth staining (in Section 4.4 of the SmPC).

All doxycycline formulations have been used in the studies submitted for review. It is noted that intravenous formulation of doxycycline was used as an intra-lesional sclerosant and not for its anti-infective indications.

IV.2 Non-clinical aspects

The MAH did not submit any non-clinical data.

IV.3 Clinical aspects

1. Introduction

The MAH submitted 20 sponsored clinical study reports which are noted below:

30-10-1: The Efficacy and Toleration of 50 mg Doxycycline in the Treatment of Acne Vulgaris. A Comparison of Doxycycline and Minocycline.

30-10-2: The Efficacy and Toleration of Doxycycline 50 mg Daily Versus Placebo in the Treatment of Acne Vulgaris.

DXC-CH-86-001: Vibramycin 50 mg in the Treatment of Facial Acne.

DXC-D-86-004: Open, Comparative Study of Oral Doxycycline 50 mg/day vs Minocycline 100 mg/day in the Management of Facial Acne Vulgaris.

DXC-D-87-007: Open, Non-comparative Study on Doxycycline (50 mg PO/day) in the Therapy of Facial Acne Vulgaris.

DXC-F-90-001: A Study of the Efficacy and Tolerance of Low-Dose Oral Doxycycline Monohydrate, Taken for a Period of Two and a Half Months, in Patients with Refractory Acne Vulgaris.

DXC-IND-87-003: To study the efficacy and safety of doxycycline 50 mg in the treatment of acne vulgaris.

DXC-P-87-001: Efficacy and Safety of Doxycycline in Facial Acne Vulgaris.

DXC-IND-87-001: A Double-Blind Study in the Treatment of Acne Vulgaris with Vibramicina (Doxycycline).

DXC-UK-85-001-121: Efficacy and Safety of Doxycycline in Facial Acne Vulgaris.

DXC-FWA-89-003: Study of Efficacy and Toleration of Vibramicina 200 in the Treatment of Sinusitis.

DXC-II-94-001: Clinical Efficacy and Toleration of Doxycycline Monohydrate Dispersible Tablets in the Treatment of Acute Purulent Sinusitis.

DXC-FWA-86-001: Vibramycin in the Treatment of Sinusitis in Adult Patients.

DXC-RCI-89-001: Study of Efficacy and Toleration of VIBRA 200 in the Treatment of Sinusitis.

DXC-B-93-001: Open Randomized Study Comparing Doxycycline and Amoxiclav in the Treatment of Acute Suppurative Tracheobronchitis in Adult Patients.

DXC-P-86-002: Treatment of Acute Respiratory Tract Infections with a New Formulation of Doxycycline.

DXC-P-91-001: Open, Non-Comparative Study to Assess the Efficacy and Tolerance of Doxycycline in the Treatment of Acute Respiratory Infections.

DXC-II-94-002: Clinical Efficacy and Tolerability of Doxycycline (Vibramicina) in Acute Lower Respiratory Tract Infections (LRTI).

DXC-FWA-89-001: Study of Efficacy and Toleration on Doxycycline in the Treatment of Vaginitis.

DXC-FWA-89-002: Study of Efficacy and Toleration of Vibra 200 for the Treatment of Recent Acute Urethritis in Men.

Additionally, the MAH performed studies DXC-CH-86-002, DXC-F-88-001, DXC-FWA-88-001, DXC-GAB-84-006 and DXC-TUN-88-001, however they were not able to retrieve any information pertaining to use in children, and thus no data were submitted for review.

The MAH also submitted studies based on a literature search using the following search criteria: doxycycline, humans, all infant: birth to 23 months, all child: 0 to 18 years, newborn: birth to 1 month, infant: 1 to 23 months, preschool child: 2 to 5 years, child: 6 to 12 years, adolescent: 13 to 18 years.

The search identified 1654 published article abstracts, which were then individually reviewed for relevance. A summary of the 52 relevant articles is provided, listed per treatment indication:

Acne

Babaeinejad, Shahla, Effat Khodaeiani, and Rohollah Fadaei Fouladi. "Comparison of therapeutic effects of oral doxycycline and azithromycin in patients with moderate acne vulgaris: What is the role of age?" Journal of Dermatological Treatment 22.4 (2011): 206-210.

Leyden, James J., et al. "A randomized, phase 2, dose-ranging study in the treatment of moderate to severe inflammatory facial acne vulgaris with doxycycline calcium." Journal of drugs in dermatology: JDD 12.6 (2013): 658-663.

Moore, A., Ling, M., Bucko, A., Manna, V., & Rueda, M. J. (2015). Efficacy and Safety of Subantimicrobial Dose, Modified-Release Doxycycline 40 mg Versus Doxycycline 100 mg Versus Placebo for the treatment of Inflammatory Lesions in Moderate and Severe Acne: A Randomized, Double-Blinded, Controlled Study. Journal of drugs in dermatology: JDD, 14(6), 581-586.

Parish, Lawrence Charles. "The treatment of acne vulgaris with low dosage doxycycline." Acta Dermatovenerologica Croatica 13.3 (2005): 0-0.

Ullah, Ghafoor, et al. "Comparison of oral azithromycin with oral doxycycline in the treatment of acne vulgaris." J Ayub Med Coll Abbottabad 26.1 (2014): 64-7.

Lyme disease

Bremell, Daniel, and Leif Dotevall. "Oral doxycycline for Lyme neuroborreliosis with symptoms of encephalitis, myelitis, vasculitis or intracranial hypertension." European Journal of Neurology 21.9 (2014): 1162-1167.

Dattwyler, Raymond J., et al. "Ceftriaxone compared with doxycycline for the treatment of acute disseminated Lyme disease." New England Journal of Medicine 337.5 (1997): 289-295.

Karlsson, M., et al. "Concentrations of doxycycline and penicillin G in sera and cerebrospinal fluid of patients treated for neuroborreliosis." Antimicrobial agents and chemotherapy 40.5 (1996): 1104-1107.

Karlsson, M., et al. "Comparison of intravenous penicillin G and oral doxycycline for treatment of Lyme neuroborreliosis." Neurology 44.7 (1994): 1203-1203.

Nadelman, Robert B., et al. "Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite." New England Journal of Medicine 345.2 (2001): 79-84.

THORSTRAND, CARITA, et al. "Successful treatment of neuroborreliosis with ten day regimens." The Pediatric infectious disease journal 21.12 (2002): 1142-1145.

Malaria

Pang, LorrinW, et al. "Doxycycline prophylaxis for falciparum malaria." The Lancet 329.8543 (1987): 1161-1164.

Ponnampalam, J. T. "Doxycycline in the treatment of falciparum malaria among aborigine children in West Malaysia." Transactions of the Royal Society of Tropical Medicine and Hygiene 75.3 (1981): 372-377.

Weiss, Walter R., et al. "Daily primaquine is effective for prophylaxis against falciparum malaria in Kenya: comparison with mefloquine, doxycycline, and chloroquine plus proguanil." Journal of Infectious Diseases 171.6 (1995): 1569-1575.

Other Parasitic Infections

Coulibaly, Yaya I., et al. "A randomized trial of doxycycline for *Mansonella perstans* infection." New England Journal of Medicine 361.15 (2009): 1448-1458.

Debrah, Alexander Yaw, et al. "Macrofilaricidal effect of 4 weeks of treatment with doxycycline on *Wuchereria bancrofti*." Tropical Medicine & International Health 12.12 (2007): 1433-1441.

Supali, Taniawati, et al. "Doxycycline Treatment of *Brugia malayi*—Infected Persons Reduces Microfilaremia and Adverse Reactions after Diethylcarbamazine and Albendazole Treatment." Clinical infectious diseases46.9 (2008): 1385-1393.

Taylor, Mark J., et al. "Macrofilaricidal activity after doxycycline treatment of *Wuchereria bancrofti:* a double-blind, randomised placebo-controlled trial. "The Lancet 365.9477 (2005): 2116-2121.

Turner, Joseph D., et al. "Macrofilaricidal activity after doxycycline only treatment of *Onchocerca volvulus* in an area of Loa co-endemicity: a randomized controlled trial." PLoS Negl Trop Dis 4.4 (2010): e660.

Genito-urinary Infections

Geisler, William M., et al. "Azithromycin versus doxycycline for urogenital *Chlamydia trachomatis* infection." New England Journal of Medicine 373.26 (2015): 2512-2521.

Gjønnæss, Halvard, and Eirik Holten. "Doxycycline (Vibramycin®) in Pelvic Inflammatory Disease." Acta obstetricia et gynecologica Scandinavica 57.2 (1978): 137-139.

Khosropour, Christine M., et al. "Suboptimal adherence to doxycycline and treatment outcomes among men with non-gonococcal urethritis: a prospective cohort study." Sexually transmitted infections 90.1 (2014): 3-7.

Thorpe, E. M., et al. "Chlamydial cervicitis and urethritis: single dose treatment compared with doxycycline for seven days in community based practises." Genitourinary medicine 72.2 (1996): 93-97.

Respiratory tract Infections

Casado, M. J. "Doxycycline in respiratory tract infections. Report of a retrospective study in Spain during the winter 1972-1973." Chemotherapy 21 (1974): 76-90.
Herz, G., and J. Gfeller. "Sinusitis in paediatrics." Chemotherapy 23.1 (1977): 50-57.

Lung, David Christopher, et al. "Rapid Defervescence After Doxycycline Treatment of Macrolide-resistant *Mycoplasma pneumoniae*–Associated Community-acquired Pneumonia in Children." The Pediatric infectious disease journal 32.12 (2013): 1396-1399

Okada, Takafumi, et al. "Rapid effectiveness of minocycline or doxycycline against macrolide-resistant *Mycoplasma pneumoniae* infection in a 2011 outbreak among Japanese children." Clinical infectious diseases (2012): cis784.

Pestel, M. "Doxycycline in the Treatment of Respiratory Tract Infections." Chemotherapy 21.Suppl. 1 (1975): 91-108.

Richards, J. G. "Doxycycline and amoxycillin in respiratory infections: a comparative assessment in general practice." *Current medical research and opinion* 6.6 (1980): 393-397.

Rickettsial Diseases

Alvarez-Hernandez, Gerardo, et al. "Clinical profile and predictors of fatal Rocky Mountain spotted fever in children from Sonora, Mexico." The Pediatric infectious disease journal 34.2 (2015): 125-130.

Bhat, Nowneet Kumar, et al. "Scrub typhus: A common rickettsial disease emerging in a new geographical region of north India." Journal of Pediatric Infectious Diseases 9.2 (2014): 93-99.

Chanta, Chulapong, and Suwalee Chanta. "Clinical study of 20 children with scrub typhus at Chiang Rai Regional Hospital." JOURNAL-MEDICAL ASSOCIATION OF THAILAND 88.12 (2005): 1867.

Meloni, Gianfranco, and Tullio Meloni. "Azithromycin vs. doxycycline for Mediterranean spotted fever." The Pediatric infectious disease journal 15.11 (1996): 1042-1044.

Nawab, Tanveer, S. Srinivasa, and Sai Praneeth Reddy. "A clinical study of rickettsial disease and its manifestations." Current Pediatric Research 19 (2015).

Palanivel, Sengottaiyan, et al. "Clinical profile of scrub typhus in children." The Indian Journal of Pediatrics 79.11 (2012): 1459-1462.

Perine, P. L., et al. "Single-dose doxycycline treatment of louse-borne relapsing fever and epidemic typhus." The Lancet 304.7883 (1974): 742-744.

Yagupsky, Pablo, et al. "Comparison of two dosage schedules of doxycycline in children with rickettsial spotted fever." Journal of Infectious Diseases 155.6 (1987): 1215-1219.

Leptospirosis

Phimda, Kriangsak, et al. "Doxycycline versus azithromycin for treatment of leptospirosis and scrub typhus." Antimicrobial agents and chemotherapy 51.9 (2007): 3259-3263.

Suputtamongkol, Yupin, et al. "An open, randomized, controlled trial of penicillin, doxycycline, and cefotaxime for patients with severe leptospirosis." Clinical Infectious Diseases 39.10 (2004): 1417-1424.

Trachoma

Darougar, S., et al. "Family-based suppressive intermittent therapy of hyperendemic trachoma with topical oxytetracycline or oral doxycycline. “British Journal of Ophthalmology 64.4 (1980): 291-295.

Hoshiwara, Isao, et al. "Doxycycline treatment of chronic trachoma." JAMA224.2 (1973): 220-223.

Plague

Mwengee, William, et al. "Treatment of plague with gentamicin or doxycycline in a randomized clinical trial in Tanzania." Clinical infectious diseases 42.5 (2006): 614-621.

Cholera

Alam, A. N., et al. "Randomised double blind trial of single dose doxycycline for treating cholera in adults." Bmj 300.6740 (1990): 1619-1621.

Sclerotherapy

Bansal, Abhishek, et al. "Doxycycline sclerodesis as a treatment option for persistent Morel-Lavallée lesions." Injury 44.1 (2013): 66-69.

Burrows, Patricia E., et al. "Percutaneous sclerotherapy of lymphatic malformations with doxycycline." Lymphatic research and biology 6.3-4 (2008): 209-216.

Cahill, Anne Marie, et al. "Percutaneous sclerotherapy in neonatal and infant head and neck lymphatic malformations: a single center experience." Journal of pediatric surgery 46.11 (2011): 2083-2095.

Chaudry, Gulraiz, et al. "Sclerotherapy of abdominal lymphatic malformations with doxycycline." Journal of Vascular and Interventional Radiology 22.10 (2011): 1431-1435.

Shiels, William E., Allan C. Beebe, and Joel L. Mayerson. "Percutaneous Doxycycline Treatment of Juxtaphyseal Aneurysmal Bone Cysts." Journal of Pediatric Orthopaedics 36.2 (2016): 205-212.

Shiels W, Murakami J. Directed tumoral therapy of aneurysmal bone cysts in children. Pediatr Radiol 2011; 41(Suppl):S283.

Tooth staining

Todd, Suzanne R., et al. "No visible dental staining in children treated with doxycycline for suspected Rocky Mountain spotted fever." The Journal of pediatrics 166.5 (2015): 1246-1251.

Volovitz, Benjamin, et al. "Absence of tooth staining with doxycycline treatment in young children." Clinical pediatrics 46.2 (2007): 121-126.

Other:

Herz, G., and J. Gfeller. "Vibramycin in paediatrics." Chemotherapy 21.Suppl. 1 (1975): 58-67.

2. Clinical studies

The indications studied in the 20 MAH-sponsored studies were acne (10 studies), sinusitis (4 studies), acute respiratory infection (2 studies), acute suppurative tracheobronchitis (ASTB), vaginitis, acute urethritis and acute lower respiratory tract infection (1 study each). Each study was individually assessed but they were grouped by clinical indication for the discussion.

The clinical studies from the literature search were also individually reviewed but grouped together by indication in the discussion of doxycycline's efficacy and safety. The tabulated clinical summary is included below for each indication.

Summary of Clinical Studies:
Table 2: Acne

Study Number **Year of the Study Study Design and Objective (s)**	**Total Number of Patients (Age Range)** **Total Number of Paediatric Patients (Age Range)**	**Regimen: Formulation, Dose and Duration of the Treatment**	**Baseline data** **Efficacy Results** **Safety Results**
30-10-1 1986 Single-blind, parallel-group, comparative study The objective of this study was to compare the efficacy and tolerability of doxycycline 50 mg daily with minocycline 50 mg twice a day, in the treatment of moderate-to-severe acne (acne major).	21 (12-29) 9 (12-18)	**Regimen 1:** Doxycycline 50 mg capsule once daily for 11 to 14 weeks	Patient assessment of efficacy was determined to be excellent by 33% of patients in the doxycycline group and 16% patients in the minocycline group. Efficacy was good-to-excellent for 73% and 84% of doxycycline and minocycline treated patients, respectively. However, there was no statistically significant difference in efficacy between the 2 drugs. Overall assessment of efficacy was found to be similar between the doxycycline and minocycline treatment groups. Overall assessment of tolerability as determined by the patient was stated to be excellent by 53% and 37% patients in the doxycycline and minocycline group, respectively, and assessed as fair by 7% and 21% patients in the doxycycline group and minocycline group, respectively. No information is available regarding the AEs. **Patients enrolled were Age ≥12 years with over half of the patients less than 18 years old.**
	22 (14-35) 13 (14-18)	**Regimen 2:** Minocycline 50 mg twice a day for 10 to 15 weeks	
30-10-2 1986 Randomised, double-blind, parallel-group study The objective of this study was to compare the efficacy and tolerability of a 50-mg daily dose of doxycycline with matching placebo, in the treatment of moderate-to-severe acne (acne major) over a 12-week period.	26 (17-41) 6 (17-18)	**Regimen 1:** Doxycycline 50 mg capsule once daily for 11 to 16 weeks.	The reduction in number of lesions was significantly greater in the doxycycline group than in placebo group. The patient's assessment of efficacy at the end of therapy was determined to be excellent by 32% of patients in the doxycycline group compared with none in the placebo group and assessed as good to excellent by 77% of patients in the doxycycline group compared with 27% patients in the placebo group. The difference in efficacy between the 2 groups was significant ($p \leq 0.005$). All the patients in both the treatment groups reported either good or excellent tolerability to the trial medication. There was no statistically significant difference in tolerability between doxycycline and placebo. **Patients were ≥16years with a quarter of the patients < 18 years. No comments about specific adverse events.**
	25 (16-37) 8 (16-18)	**Regimen 2:** Matching placebo for 11 to 13 weeks.	

DXC-CH-86-001 1987 Open-label study The objective of the study was to expand the data based on the safety and efficacy of doxycycline 50 mg when given once daily for 3 months in patients suffering from facial inflammatory lesions of acne.	40 (13-42) 22 (13-18)	One (1) tablet of 50 mg doxycycline once daily for 3 months with control examinations scheduled at Months 1 and 3.	During the 12-week observation period, the mean number of total lesion counts decreased from 22.9 (range 7-73) to 8.8 (range 0-43) at the end of study. The overall mean reduction of inflammatory lesions was 62% during the 3-month observation period. The result showed a further improvement in inflammatory lesions occurring between the first and third month of treatment. The mean count of non-inflammatory lesions (comedones) also decreased from 22.5 at baseline to 14.3 after 3 months' treatment. Overall assessment of efficacy was judged as excellent or good in 28 cases by the physician and in 30 cases by patients themselves. Overall efficacy was rated fair by 6 and 4 cases by physicians and patients, respectively, and it was judged as poor in 6 cases. Four (4) AEs, all of mild intensity were reported by 3 patients: diarrhoea in 2 patients and vaginal candidiasis in another. Fatigue was also reported by 1 of the 2 patients reporting diarrhoea. The cases of diarrhoea did not necessitate treatment, but the patient with vaginal candidiasis was given topical intravaginal treatment. **Patients enrolled were ≥13 years with half under 18 years old.**
DXC-D-86-004 1989 Open-label, randomised, comparative study The objective of the study was to evaluate the clinical efficacy and tolerability of a low-dose acne therapy with doxycycline 50 mg daily versus treatment with the commonly used regimen of minocycline 100 mg daily.	50 (15-36) Not available	**Regimen 1:** One (1) tablet of doxycycline 50 mg once daily as a single dose, for 12 weeks.	After the completion of treatment, cure was achieved in 8% of patients, improvement in 70% of the patients and therapeutic results were assessed as poor in 22% of patients in the doxycycline group. In comparison to this the following results were obtained in patients treated with monocycline: 6% of the patients were cured, 76% improved, and therapeutic failure occurred in 18% of patients. In doxycycline group, therapeutic results were graded as excellent or good in 62% of patients, satisfactory in 16 % of patients and poor in 22% of patients. In the minocycline group, results of therapy were assessed as excellent or good in 62%, as satisfactory in 18% and poor in 20% of patients. The results did not show significant difference in the clinical efficacy between therapy with doxycycline in a daily dose of 50 mg and 100 mg minocycline daily for the treatment of acne vulgaris. Explorative data analysis revealed comparable efficacy and tolerability of acne therapy with doxycycline 50 mg daily and minocycline 100 mg daily. Seventeen (17) patients reported AEs during therapy, 8 patients from the minocycline group and 8 of 9 patients from the doxycycline group. Majority were gastrointestinal disorders. Six (6) patients from each group discontinued the treatment because of adverse reactions except
	50 (15-36) Not available	**Regimen 2:** Minocycline 50 mg twice a day, for 12 weeks.	

			1 female patient in the minocycline group, who discontinued because of planned pregnancy. **Patients≥ 15yrs, Paediatric numbers were not known.**
DXC-D-87-007 1987 Open-label, non-comparative study The objective of this study was to evaluate clinical efficacy and tolerability of an acne therapy with a daily dosage of 50 mg doxycycline after a treatment period of 12 weeks.	70 (13-35) Not available	Doxycycline 50 mg dose daily (1 tablet = 100 mg tablet with break line) for 12 weeks.	Overall assessment of therapy was excellent in 23.9% of patients, good in 28.4%, satisfactory in 26.9% and poor in 20.9% of patients. The results supported the conclusion that therapy with doxycycline was efficacious and well-tolerated. Tolerability of long-term therapy was excellent. Adverse drug reaction occurred in only 1 patient, who presented with mild nausea, which resolved without any treatment. **Patients recruited were ≥13y, but paediatric numbers not known.**
DXC-F-90-001 1991 Open-label, multicentre study To confirm the efficacy and tolerability of a new formulation of doxycycline monohydrate (divisible tablets of 100 mg) in relation to the effects on inflammatory lesions, in subjects presenting with refractory acne vulgaris.	106 (15-44) Not available	A 100 mg daily dose (100 mg divisible tablets) for the first 14 days followed by 50 mg daily for the following 2 months, to complete the treatment period of 75 days.	Overall clinical outcome was assessed as satisfactory in more than 95% of cases at both Day 14 and Day 75. A statistically significant ($p = 0.0001$) reduction in the severity of the disease and the number of lesions was observed at Day 14, which was sustained at Day 75. The effects in inflammatory lesions were assessed as good in 62% and 52% of cases at Day 14 and Day 75, respectively. Similarly, the results were assessed as moderate in 37% and 46% of cases at Day 14 and Day 75, respectively. Study treatment also prevented the development of new acneic eruptions in 79.5% of cases during the study. AEs were reported in 12 subjects, all were non-serious and majority were gastrointestinal disorders. **Patients recruited were ≥ 15yr, paediatric numbers not known. No new signals reported.**
DXC-IND-87-001 1988 Double-blind study To evaluate the efficacy of a low dose of doxycycline in the treatment of acne vulgaris.	25 (15-43) Not available	**Regimen 1:** Single 50 mg once daily dose of doxycycline capsule (50 mg capsule) for 12 weeks.	The efficacy of doxycycline was analysed every week by observing the clinical improvement. A significant ($p<0.05$) clinical improvement was seen from the eighth week onwards in 84% (21 out of 25 patients) of patients in the doxycycline group and 12.5% (2 out of 16 patients) of patients in the placebo group. The effectiveness of doxycycline 50 mg was observed to be increasing in the tenth week (92%) and 12th week (96%). AEs were observed in 2 patients: hair loss observed in 1 patient and fluor albus in the other patient.
	16 (15-43) Not available	**Regimen 2:** Matching placebo for 12 weeks.	

			Enrolled participants were aged ≥ 15 years but number of paediatric patients not known. Improvement assessment scale not provided.
DXC-IND-87-003 1989 Double-blind parallel study To compare the efficacy and safety of doxycycline 50 mg daily with placebo in the treatment of acne vulgaris.	32 (15-39) Age ≥ 15 recruited but only 5 (15-18)	**Regimen 1:** A 50 mg once daily dose of doxycycline (50 mg capsule) for 12 weeks.	The results showed good improvement in 9 (28.1%) doxycycline-treated patients and in 2 (6.9%) placebo-treated patients, moderate improvement was seen in 13 (40.6%) patients who received doxycycline and 6 (20.7%) patients who received placebo. A slight improvement was observed in 7 (21.9%) patients who received doxycycline and in 9 (31%) patients who received placebo and no improvement was seen in 3 (9.4%) patients who received doxycycline and 12 (41.4%) patients who received placebo. A significant difference ($p<0.01$) in efficacy was observed between doxycycline and placebo. Five (5) AEs were reported in 6 patients during the treatment: hyperpigmentation (2 cases), headache, miliaria, reduced period and palpitation (1 case each). All the AEs were mild in intensity except for 1 (reduced period) reported in 1 patient, which was of severe intensity and was considered unrelated to the study drug. **Patients aged ≥ 15 years recruited but only 5 were15 years to 18yrs. The assessment scale for acne improvement not provided.**
	29 (15-39)	**Regimen 2:** Placebo for 12 weeks.	
DXC-P-87-001 1990 Open-label, non-comparative study To evaluate the tolerability and efficacy of doxycycline using 50 mg dispersible tablets in the treatment of acne vulgaris.	50 (13-36) Paediatric numbers not available for Age ≥ 13y	A single 50 mg once daily dose of doxycycline (50 mg dispersible tablets) for 12 weeks.	After 12 weeks, no clinical improvement was observed in 4 (8%) patients. Marked improvement was observed in 18 (36%) patients, a complete absence of lesions was observed in 28 (56%) patients. With respect to the efficacy of the drug as evaluated by the investigators, the results were considered excellent in 7 (14%) subjects, good in 29 (58%), poor in 3 (6%), and its action was deemed fair in the remaining 11 (22%) subjects. The overall efficacy observed by the subjects was excellent or good in 34 (68%) patients, and fair in the remaining 16 (32%) patients. Based on subject evaluation degree of severity was considered mild in 15 (30%) patients, moderate in 23 (46%) patients and severe in 12 (24%) patients. Good tolerance was observed in 28 (55%) patients and excellent in the remaining 22 (45%) patients. No AEs were observed. **Paediatric numbers not available for those ≥ 13 years.**

Rapporteur's comments:

Although the MAH provided summaries for 10 studies in acne, only nine (9) studies were assessed; study DXC-UK-85-001-121 was excluded from analysis as the submitted file contained a different study. In the 9 acne studies reviewed, 5 included comparators (either minocycline or placebo), and all included paediatric patients, with the lowest recruitment age being 12 years. Only 6 study reports clarified the numbers of paediatric patients enrolled. None of the studies provided separate analysis of the paediatric data.

Overall doxycycline was superior to placebo and at least non-inferior to the other antibiotic comparator used. Improvement in acne after doxycycline use was also documented in the non-comparative studies performed.

With regards to safety, only one study did not report any safety data. In the other studies, mild adverse events (AEs) were reported and were mostly gastrointestinal in origin. Overall doxycycline was described as well tolerated.

Table 3: Respiratory infections

DXC-FWA-86-001 1988 Open-label, non-comparative, multicentre study The aim of this study was to assess the clinical efficacy and tolerability of doxycycline in the treatment of sinusitis. (Ivory Coast)	152 (9-65) Not available	In acute sinusitis and acute attacks of chronic sinusitis: A 200 mg daily dose (doxycycline 100 mg tablets) for 8 days. In chronic sinusitis: a follow-up treatment was administered in 50 patients; 80% of patients were treated with 100 mg daily whereas the remaining 20% patients were treated with 200 mg doxycycline daily, both treated for 5.9 days (SD = 1.8).	The efficacy of the drug was assessed on the basis of number of days required to return the temperature to normal, and resolution of other clinical parameters like local pain, oedema, suppuration, cephalalgia and bacteriological data if available. Apyrexia was achieved within 4 days of treatment. There was total disappearance of clinical parameters like local pain (5.2 days), oedema (5.7 days), suppuration (7.2 days) and cephalalgia (5.8 days). The overall efficacy was assessed to be very good or good in 90% of patients. Tolerability was assessed as very good or good for 96% of patients. Three (3) AEs were reported (1.9%), mainly nausea. **Study aimed to treat sinusitis in adults and to recruit patients 16yrs and over. However, patients ≥ 9 years were included but number of paediatric patients not known.**
DXC-FWA-89-003	44 (16-56) 2 (16-17)	In acute sinusitis and	Overall assessment of efficacy was cure in 56.1%, improvement in 34.1%, having an effective

1990 Open-label, non-comparative study To assess the clinical efficacy and tolerability of doxycycline in the treatment of sinusitis.		acute attacks of chronic sinusitis: A 200 mg once daily dose of doxycycline for 8 to 16 days.	treatment in 90.2% and failure in 9.8% of patients. Overall assessment of tolerability showed very good or good results in 85.7% patients, fair in 9.5% patients and poor in 4.8% patients. Ten (10) AEs were reported, which included nausea (3), diarrhoea (2), abdominal pain, headache, vomiting, drowsiness and asthenia (1 each). One (1) patient withdrew on the fourth day of treatment because of intolerance. Age ≥ 16y but only two paediatric patients SAT AE similar to what is expected for the drug average to mild.
DXC-II-94-001 1995 Prospective, open-label, non-comparative study To assess the clinical efficacy and tolerance of doxycycline monohydrate 200 mg tablets, administered on Day 1 followed by 100 mg once daily for 10 to 14 days, in the treatment of acute purulent sinusitis; to assess the microbial isolates recovered from the patients and their in-vitro susceptibility to 4 commonly used antimicrobials.	159 (12-60) Paediatric numbers not available	A single 200 mg once daily dose of doxycycline monohydrate (Vibazine DT; 200 mg tablet) for 1 day, followed by 100 mg once daily dose (100 mg tablet) for 10 to 14 days.	The overall evaluation showed excellent or good response in about 84.67% of patients. Resolution of abnormal radiological signs was observed in 50% of the patients. Gram-positive and/or gram-negative organisms were observed in only 50% of the smears from nasal discharge. In vitro sensitivity showed that 65% of isolates were sensitive to doxycycline and 35% were resistant strains. Correlating in vitro sensitivity with the clinical outcome, the incidence of false resistance was found to be as high as 78.8%. The incidence of false sensitivity was 5%. Doxycycline was well tolerated by all the patients, however, 5 patients experienced AEs. Four (4) patients had mild gastrointestinal upset. One (1) patient was withdrawn from the study because of hypersensitivity reaction in the form of urticaria.
DXC-RCI-89-001 1990 Open-label, non-comparative study To assess the clinical efficacy and tolerance of doxycycline in the treatment of sinusitis.	44 (16-56) 2 (16-17)	In acute sinusitis and acute attacks of chronic sinusitis: A 200 mg once daily dose of doxycycline (200 mg tablet) for 8 to 16 days.	The overall efficacy rate showed a success of 90.2% with cure in 23 (56.1%), improvement in 14 (34.1%) and failure in 4 (9.8%) cases. Tolerability was assessed as very good or good in in 36 (85.7%) patients, fair in 4 (9.5%) patients and poor in 2 (4.8%) patients. Out of 44 patients, 10 patients experienced AEs including nausea (3 cases), diarrhoea (2 cases), abdominal pain (1 case), headache (1 case), vomiting (1 case), drowsiness (1 case) and asthenia (1 case) during the study of which 2 cases were mild, 5 were average and 2 were important (headache and asthenia). One (1) patient was withdrawn from the study due to intolerance **Only patients Age ≥16 years were recruited although inclusion criteria was for ≥ 8yrs.**
DXC-II-94-002	131 (12-80)	A single	The overall evaluation, based on clinical

1996 Prospective, open-label, non-comparative, multicentre study To assess the clinical efficacy and tolerability of doxycycline monohydrate 200 mg tablets (Vibazine DT), administered on Day 1 followed by 100 mg once daily for 7 to 10 days, in the treatment of acute LRTI including acute bronchitis, acute exacerbation of chronic bronchitis and acute bronchopneumonia. To evaluate the aetiology and sensitivity pattern, microbial isolates from sputum of the patients identified before treatment and in vitro susceptibility to 5 commonly used antimicrobials was tested.	7 (12-18).	200 mg once daily dose of doxycycline monohydrate. (Vibazine DT; 200 mg tablet) for 1 day, followed by 100 mg tablet once daily for 7 to 10 days.	improvement showed excellent or good response in 92% of patients. The clinical success was equally high in individual subgroups; 93% in acute bronchitis, 89% in acute exacerbations of chronic bronchitis and 95% in bronchopneumonia. In vitro sensitivity reports showed that 70% of isolates were sensitive to doxycycline with an incidence of true sensitive reports of 91.3% whereas the incidence of true resistance was 14.3%. Thus, there was a high incidence of false resistance. Tolerance was assessed in all 131 patients with AEs reported in only 2 patients. One (1) patient with COPD and cardiac heart failure was enrolled in the trial. On the second day, cardiac failure worsened and the patient was withdrawn from the study; the patient died because of cardiac complication on the third day following the withdrawal. Death was not related to doxycycline as per the Investigator. Apart from this, 1 patient developed gastritis. **Patients aged ≥ 12 years were enrolled with only 7 (12-18) included in final report.**
DXC-P-86-002 1988 Open-label, non-comparative multicentre study To characterise the onset of action, potency and efficacy of doxycycline using 100 mg dispersible tablets in the treatment of acute respiratory tract infections.	775 (8 or older) 26 (8-12); 76 (13-20)	**Regimen 1:** A 100 mg once daily dose of doxycycline 100 mg dispersible tablets for 10 days. **Regimen 2:** A 200 mg once daily dose of doxycycline (two 100 mg dispersible tablets) for 10 days. **Regimen 3:** A 200 mg dose, twice a day, of doxycycline (two 100 mg dispersible tablets at each	A total of 92.8% of cases showed very good or good efficacy, 6.06% cases showed results as fair, 0.64% cases showed nil efficacy and efficacy was not reported in 0.38% cases. The cumulative percent of patients with no expectoration was observed on Day 2 (11.76), Day 5 (30.82), Day 10 (71.52) and after 15 days, no patients had expectoration and cough. The safety results in 709 (91.5%) patients showed very good or good tolerability, 47 (6.06%) patients showed fair tolerability, 16 (2.06%) patients showed poor tolerability and tolerability was not reported in 3 (0.38%) patients with tracheitis, acute bronchitis and sinusitis. No specific AE reported **Age enrolled were ≥ 8 years though actual numbers < 18 years are not known.**

		dose) for 10 days.	
DXC-P-91-001 1992 Open-label, non-comparative study To assess the efficacy and tolerability of doxycycline in the treatment of acute respiratory infections.	875 (10-86) 44 (10-18)	Adults: A 100 mg twice a day dose (100 mg dispersible tablets) for 2 to 24 days.	Out of 875 patients, 861 were clinically cured, 7 improved and in 7 cases treatment was unsuccessful. Tolerance was considered as very good or good in 834 patients, reasonable in 32 patients and poor in 9 patients. Forty (40) of 875 patients experienced AEs which included abdominal discomfort, epigastralgia, diarrhoea, nausea, pyrosis, vomiting, dyspepsia, headache/tinnitus, anorexia and toxic dermatitis during the study. Nineteen (19) AEs were considered moderate and 21 were considered mild in intensity. **Age ≥ 8 in study but only patients ≥ 10 years enrolled. Less than 5% were paediatric patients**.
DXC-B-93-001 1994 Open-label, randomised, comparative study The purpose of this study was to compare the efficacy, tolerability and duration of treatment of 2 antibiotics, i.e., oral doxycycline 100 to 200 mg daily versus Amoxiclav 500 + 125 mg 3 times a day, in the treatment of acute suppurative tracheobronchitis (ASTB).	104 (15-75) (Mean age 51.2 ± 1.6) Not available	**Regimen 1:** Doxycycline tablets 200 mg on Day 1, followed by 100 mg tablets daily for the remainder of the treatment duration. Treatment was given for at least 5 days. **Regimen 2:** Doxycycline tablets 200 mg daily for at least 5 days of treatment.	Clinical response rates to treatment were comparable for the 2 treatment groups with 89% for the doxycycline group and 91% for amoxiclav group. Ten (10) patients in the doxycycline group and 8 patients in the amoxiclav group were switched to the alternative group because of inadequate response to initial antibiotic. No difference in the clinical results was observed between the 2 treatments. However, the number of cures remained low in this crossover group of patients. Mean time for improvement was 3.3 days for doxycycline and 3.4 days for amoxiclav. AEs were more frequent in the amoxiclav group. In the doxycycline group AEs were reported as mild in 13% and moderate in 4% of patients, and in the amoxiclav group AEs were reported as mild in 41 % and moderate in 23% of patients. Most commonly reported AEs were nausea, diarrhoea and abdominal discomfort. No severe AEs occurred during the study. **Numbers of paediatric patients ≥ 15years were not known.AE reported similar to what is expected for both drugs but more reported for amoxiclav.**
	106 (15-75) (Mean age 48.6 ± 1.64) Not available	**Regimen 3:** Amoxiclav tablet 500 + 125 mg 3 times a day for at least 5 days.	

Rapporteur's comments:

With regards to the use in respiratory infections, 8 studies were included: 4 for sinusitis, 3 for respiratory tract infections and one for tracheobronchitis. Two of these studies were comparator studies, one of which compared different doses of doxycycline vs amoxicillin and the other compared 3 dosing regimens of doxycycline. Four studies described the number of paediatric patients enrolled but did not perform separate analysis of the paediatric data. It is noted that one study (DXC-FWA-86-001) enrolled patients older than 9 years, although the study had a minimum age criteria of 16 years.

One comparator study reported that the efficacy of doxycycline was non-inferior to co-amoxiclav. With regards to the comparison between different doxycycline dosing regimens, no difference in efficacy was demonstrated. The largest study was an open label, non-comparator study involving over 800 patients, which demonstrated a high clinical cure rate (861/875 of patients treated), with mild to moderate adverse events (AEs).

Six (6) of the 8 studies reported adverse events, which were mostly gastrointestinal or rashes. These AEs were rated as mostly mild to moderate severity. No new paediatric adverse reactions were reported.

Table 4: Various infections

DXC-FWA-89-001 1990 Open-label non-comparative study The aim of this study was to assess efficacy and tolerability of doxycycline tablets in the curative treatment of vaginitis.	74 (17-49) 13-14 (17-20)	A 200 mg once daily dose of doxycycline for 8 to 15 days.	Overall assessment of efficacy achieved at the end of treatment was cure in 39.2% of patients, improvement in 54% and failure in about 6.8% of patients. Improvement and cure of the clinical symptoms indicates the efficacy of doxycycline in the treatment of vaginitis. Overall assessment showed very good and good tolerability in about 81.1% of patients, fair in 16.2% patients and poor in 2.7% patients. A total of 33 AEs was reported, which included nausea (10 cases), vomiting (7 cases), epigastralgia (6 cases), abdominal pain and asthenia (4 cases each) and vertigo (2 cases). Most of them were of mild intensity. Two (2) patients stopped the treatment after 3 to 5 days because of intolerance. **Paediatric numbers estimated but data for number of patients <18 years as a separate group are not available.**
DXC-FWA-89-002 1989 Open-label, single centre, non-comparative study To assess efficacy and tolerability of doxycycline in the treatment of recent acute urethritis in men.	100 (16-55) 5 (16-18)	A 200 mg once daily dose (200 mg tablet) of doxycycline for 8 to 21 days.	Overall assessment of efficacy achieved at the end of treatment showed that 95.9% subjects were cured and 4.1% of subjects failed to show the desired effect. Overall assessment made at the end of treatment showed very good tolerability to doxycycline in the treatment of acute urethritis. No AEs were reported. **Only 5 paediatric patients enrolled with an age range from 16- 18 years.**

Rapporteur's comments:

From these studies, separate analysis of paediatric data could not be performed due to the small numbers of children enrolled. Thus, no new data on safety and efficacy can be derived for these indications in the paediatric population.

All the 20 available studies involved doxycycline oral formulations. None of the studies were designed as paediatric studies, but each enrolled a small number of patients aged 8 years to younger than 18 years. A total of 3153 patients participated in the 20 available studies, out of which 2889 patients were exposed to doxycycline and the remaining 264 patients were either in the comparator group or the placebo group. Eleven (11) out of 20 studies had the information regarding the number of paediatric patients participating in the study. Two hundred and thirty-nine (239) paediatric patients (8-20[1] years old) participated in 11 studies and the number of paediatric patients involved in the remaining 9 studies was unknown. Out of 239 paediatric patients, 218 patients were exposed to doxycycline and the remaining 21 patients were either in the comparator group or the placebo group.

Overall, it was observed that doxycycline was efficacious and well tolerated for all the indications studied. None of the 20 studies were designed to evaluate differences between adults and paediatric patients, and therefore no efficacy or safety analyses were stratified by age.

Rapporteur's comments:

Although all studies included paediatric patients, not all clarified the numbers and presented the paediatric data separately, therefore further detailed analysis by age could not be done. No new paediatric indications for doxycycline have been identified in the 20 studies reviewed.

Efficacy:
In the comparator trials, superiority to placebo and at least non-inferiority to other antibiotic treatments were demonstrated but the data were not stratified by age to allow evaluation for the paediatric population.

Safety:
Paediatric safety data were not presented separately in any of the submitted study reports. In general, safety data were not reported for 3 studies and for the remainder of the submitted study reports, most the adverse events were mild to moderate in severity. Most adverse events were gastrointestinal or skin manifestations; tooth discoloration was not reported but it is noted that the follow up periods were short. No new safety signal was noted.

The studies derived from the literature search are summarised in the Table 5 below:

Table 5: Summary of Literature Articles

Article Objective(s)	**Total Patients (Age Range)**	**Treatment Regimen Total Number of Patients Per Regimen**	**Summary of Results**
Acne			

[1] In studies DXC-FWA-89-001 and DXC-P-86-002, the paediatric age range provided are 13-20 and 17-20 years respectively. As data, specifically for children aged till 18 years were not available from these studies, the paediatric age range has been included as 20 years.

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Ullah G, Noor SM, Bhatti Z, et al. J Ayub Med Coll Abbottabad 2014;26(1):64-7. To compare the efficacy of oral azithromycin with oral doxycycline in the treatment of acne vulgaris.	386 (14-30 years)	Azithromycin 500 mg daily before meal for 4 consecutive days monthly for 3 months 193 in azithromycin group. Doxycycline 100 mg daily after meals for 3 months 193 in doxycycline group.	Patients having moderate acne vulgaris on face only were assessed for the efficacy of oral azithromycin with oral doxycycline for the treatment. In the doxycycline group, 22 (11.4%) patients had an excellent response and 107 (55.4%) patients had a good response. An excellent response was noted in 6 (3.1%) in the azithromycin group, whereas a good response was observed in 44 (22.8%) patients, which made the difference between the 2 groups statistically significant. The authors concluded that azithromycin is at least as effective as doxycycline in the treatment of moderate acne vulgaris; however, in patients older than 18 years doxycycline is better.
Babaeinejad S, Khodaeiani E, Fouladi RF. Comparison of therapeutic effects of oral doxycycline and azithromycin in patients with moderate acne vulgaris: What is the role of age? J Dermatol Treat 2011;22(4):206-10.	100 (<18 years: 72 patients ≥18 years: 28 patients)	Oral azithromycin 500 mg daily, 4 consecutive days per month for 3 consecutive months Group A: 50 patients (<18 years: 34 ≥18 years: 16) Doxycycline 100 mg daily for 3 consecutive months Group D: 50 patients (<18 years: 38 ≥18 years: 12)	Patients with moderate acne vulgaris were assessed. The number and types of lesions (all over the body) were determined. It was observed that both the antibiotics were effective in the treatment of acne vulgaris, and no significant side effects were observed in Group A, whereas minor side effects were observed in Group D. Doxycycline was observed to be more effective than azithromycin in patients aged above 18 years. The authors concluded that doxycycline is more effective than azithromycin in the treatment of acne vulgaris.

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Leyden JJ, Bruce S, Lee CS, et al. A randomized, Phase 2, dose-ranging study in the treatment of moderate to severe inflammatory facial acne vulgaris with doxycycline calcium. J Drugs Dermatol 2013;12(6):658-63.	257 (12-45 years)	Doxycycline calcium tablets (40, 80 and 160 mg to achieve doxycycline doses of approximately 0.6, 1.2 and 24 mg/kg/day, respectively) Doxycycline 0.6 mg/kg: 64 Doxycycline 1.2 mg/kg: 65 Doxycycline 2.4 mg/kg: 61 Placebo: 67	At Week 12, 2.4 mg/kg/day doxycycline resulted in statistically significant decrease in inflammatory lesions compared with placebo ($p = 0.039$), whereas a trend towards an improved outcome was seen with the 1.2-mg/kg/day dose ($p = 0.075$). Statistically significant dose effect was achieved in 14.1%, 15.4% and 29.5% of patients in the 0.6-, 1.2- and 2.4-mg/kg/day doxycycline groups, respectively, compared with 16.4% in the placebo group. Adverse events were reported in 27 (42.2%), 24 (36.9%) and 27 (44.3%) patients in the 0.6-, 1.2- and 2.4-mg/kg/day treatment groups, respectively, compared with 25 (37.3%) subjects in the placebo group. Most AEs were mild-to-moderate and were considered unrelated to doxycycline. One (1) subject reported with a serious adverse event of moderate severity and was considered unrelated to the study medication. One (1) subject of the 0.6-mg/kg/day doxycycline group withdrew from the study due to treatment-related angioneurotic oedema. Three (3) subjects discontinued the study due to treatment-related adverse events: 1 subject in the placebo group due to mild vaginal infection and 2 in the 0.6 mg/kg/day doxycycline group due to mild candidiasis. Abnormal laboratory findings were reported rarely.
Parish LC, Parish JL, Routh HB, et al. The treatment of acne vulgaris with low dosage doxcycline. Acta Dermatovenerol Croat 2005;13(3):156-9.	12 (14-36 years)	Doxycycline hyclate 100 mg daily for 8 weeks. 12	Because of AE (myoclonic twitching), 1 subject withdrew from the study and 11 subjects had a 50% reduction of lesions at 8 weeks and entered into the second phase of the study. Patients received either doxycycline hyclate 20 mg twice a day or placebo in the second phase of the study. Improvement was observed in 6 subjects and no improvement in placebo group. None of the subjects completing the trial reported unwanted AEs.

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Moore A, Ling M, Bucko A, et al. Efficacy and safety of subantimicrobial dose, modified-release doxycycline 40 mg versus doxycycline 100 mg versus placebo for the treatment of inflammatory lesions in moderate and severe acne: A randomized, double-blinded, controlled study. J Drugs Dermatol 2015;14(6):581-6.	662 (12 years or older)	Sub-antimicrobial, MR-doxycycline 40 mg tablets, doxycycline 100 mg capsules or placebo once daily for 16 weeks. MR-Doxycycline: 216 Doxycycline: 224 Placebo: 222	Subjects with moderate-to-severe acne were screened. MR-doxycycline 40 mg was found to be superior to placebo in reducing the number of inflammatory lesions and percentage reduction of total lesions when compared to doxycycline 100 mg. The incidence of drug-related AEs was similar in the placebo group and the MR-doxycycline 40 mg group. MR-doxycycline 40 mg showed superior efficacy and safety to doxycycline 100 mg in the treatment of moderate-to-severe inflammatory acne.
Lyme Disease			
Nadelman RB, Nowakowski J, Fish D, et al. Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite. N Engl J Med 2001;345(2):79-84.	482 (12-82 years)	Two 100-mg capsules of doxycycline or two 100-mg capsules of placebo Doxycycline (N = 235) Placebo (N = 247)	Overall 431 subjects (89.4%) completed all 3 visits (enrollment, 3 weeks and 6 weeks). Eight (8) of 247 subjects in the placebo group (3.2%) experienced Erythema migrans at the site of the tick bite and in 1 of the 235 subjects in the doxycycline group (0.4%, $p<0.04$). Erythema migrans developed more frequently after untreated bites from nymphal ticks than after bites from adult female ticks (8 of 142 bites [5.6%] versus 0 of 97 bites [0%], $p = 0.02$). Adverse events like nausea and vomiting were more frequent in the doxycycline group 47 (30.1%) than in the placebo group 17 (11.1%). The treatment efficacy was 87% (95% confidence interval, 25-98%).

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Bremell D, Dotevall L. Oral doxycycline for Lyme neuroborreliosis with symptoms of encephalitis, myelitis, vasculitis or intracranial hypertension. Eur J Neurol 2014;21(9):1162-7. .	26 (15-85 years) with CNS symptoms and 115 (12-81 years) patients with PNS symptoms	Oral doxycycline 400 mg (median: 200-400) in CNS and PNS 141	Patients with CNS and PNS symptoms were screened. No significant decrease in mononuclear cell counts was observed between the 2 groups of patients, but a marked clinical improvement after treatment was observed in the CNS group. A decrease in CSF mononuclear cell counts in patients with Lyme neuroborreliosis with CNS symptoms was observed after treatment with oral doxycycline when compared to that of patients with Lyme neuroborreliosis with PNS symptoms.
Dattwyler RJ, Luft BJ, Kunkel MJ, et al. Ceftriaxone compared with doxycycline for the treatment of acute disseminated Lyme disease. N Engl J Med 1997;337(5):289-94. .	140 (7-85 years)	Ceftriaxone (2 g once daily [50 mg/kg of body weight, up to 2 g, in the case of children]), IV or IM, at the discretion of the investigator, for 14 days 68	In total, 58 of the 68 patients given ceftriaxone (85%) and 63 of the 72 patients given doxycycline (88%) were considered clinically cured. Eighteen (18) of 67 patients in the ceftriaxone group and 10 of 71 in the doxycycline group developed residual symptoms at their last evaluation ($p \geq 0.05$). Fourteen (14) patients in the ceftriaxone group developed arthralgia and 6 developed fatigue, whereas in the doxycycline group, 6 developed arthralgia and 5 developed fatigue. All symptoms were of mild severity. Only 1 patient in each group developed severe arthralgia. Drug-related adverse events were more frequent in the ceftriaxone group (39 of 68 patients [57%]) than in the doxycycline group (31 of 72 patients [43%], p = 0.128). Gastrointestinal events were developed more often in patients given ceftriaxone (41%) than in patients given doxycycline (25%, p = 0.049). Twenty-five (25) ceftriaxone-treated patients (37%) and

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
		Doxycycline (100 mg twice a day [4.4 mg/kg, up to 100 mg twice a day, for children weighing up to 45.5 kg]) orally for 21 days 72	4 doxycycline-treated patients (6%) developed diarrhoea (p<0.001). Only 1 patient in the ceftriaxone group had severe diarrhoea. Headache, nausea, vomiting and weight loss led to the discontinuation of doxycycline in another patient. Twice as many patients in the doxycycline group (9 [12%]) as in the ceftriaxone group (4 [6%]; p = 0.246) had dermatologic reactions, primarily photosensitivity reactions. Urticaria developed in 2 patients in each of the treatment groups. Another patient in the ceftriaxone group had angioedema (oedema of the lips, with dysphagia) after 5 days of treatment, which resolved after the discontinuation of ceftriaxone. Five (5) patients in the ceftriaxone group (7%) had mild phlebitis related to the IV line. Another patient in the ceftriaxone group discontinued therapy due to drug-induced fever. Seven (7) patients receiving ceftriaxone and 4 receiving doxycycline had minor, transient abnormalities in laboratory tests.
Karlsson M, Hammers S, Nilsson-Ehle I, et al. Concentrations of doxycycline and penicillin G in sera	46 (16-88 years)	Oral doxycycline 200 mg/day 26	Patients with a peak doxycycline concentration below the median of 6.1 μg/mL of serum had a mean concentration in CSF of 0.62 μg/mL (range, 0.5-1.0) compared with 0.97 μg/mL (range, 0.4-2.5) for patients with a higher concentration in serum. There was no significant correlation

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Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
and cerebrospinal fluid of patients treated for neuroborreliosis. Antimicrob Agents Chemother 1996;40(5):1104-7. .		3 g Penicillin G 4 times a day 20	between the concentrations of doxycycline in serum and CSF. Eleven (11) (55%) of 20 patients treated with PcG had a declining but still measurable BBB dysfunction at Day 13 of treatment, with a mean CSF/serum albumin ratio of 0.015 (range, 0.009-0.023; upper normal value, 0.008). Fourteen (14) (54%) of 26 patients treated with doxycycline had a BBB dysfunction at Day 13, with a mean CSF/serum albumin ratio of 0.016 (range, 0.009-0.035). The mean concentrations of doxycycline in CSF were similar in patients with BBB dysfunction (mean, 0.77 [range, 0.4-2.5] μg/mL) and those without BBB dysfunction (mean, 0.83 [range, 0.4-1.6] μg/mL). There was no significant correlation between the albumin ratio and the concentration of doxycycline in CSF. All patients improved during antibiotic treatment and showed no symptoms of relapse during the follow-up. One (1) patient treated with PcG and 1 treated with doxycycline were retreated with antibiotics because of residual pain after 4 months and 2 weeks, respectively. The number of patients with some residual symptoms at the end of treatment and during follow-up at 3, 6, 9 and 12 months did not differ significantly between patients with concentrations of PcG or doxycycline above and below the median concentrations in serum and CSF (Fisher exact test; p>0.05).
Thorstrand C, Belfrage E, Bennet R, et al. Successful treatment of neuroborreliosis with ten day regimens. Pediatr Infect Dis J 2002;21(12):1142-5.	203 (4.6-8.6 years)	Beta-lactam (benzylpenicillin 100 mg/kg/24 hours, cefotaxime 100 mg/kg/24 hours or ceftriaxone 100 mg/kg/24 hours, maximum dose 2 g/24 hours) Fifty-three (53) children received benzylpenicillin, 19 received cefotaxime, 109 received ceftriaxone	At the end of treatment, 58% of the children and after 2 months, 92% of the children had no symptoms. CSF findings had no statistically significant influence on the outcome. The prognosis of neuroborreliosis in children seems to be excellent with any of the 10-day treatment regimens used. The response to therapy is rapid, and improvement continues after its discontinuation. Oral doxycycline was as effective as intravenous β-lactams for the treatment and prevention of late manifestations of acute disseminated Lyme disease.

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
		Oral doxycycline therapy (4 mg/kg/24 hours, maximum dose 200 mg/24 hours) 22	
Karlsson M, Hammers-Berggren S, Lindquist L, et al. Comparison of intravenous penicillin G and oral doxycycline for treatment of Lyme neuroborreliosis. Neurology 1994;44(7):1203-7	54 (16-88 years)	IV Penicillin G (3 g/6 hours) patients for 14 days 23 Patients (IV penicillin G group) Oral doxycycline (200 mg q 24 hours) for 14 days 31 Patients (doxycycline group).	Patients with neuroborreliosis were assessed for the efficacy of oral doxycycline and IV penicillin G for the treatment. Twenty-three (23) patients were treated with IV penicillin G (3 g q 6 hours) and 31 patients were treated with oral doxycycline (200 mg/24 hours). Improvement was observed in both the groups with no significant difference in patient scoring, CSF analysis, serological and clinical follow-up. The authors concluded that oral doxycycline is an adequate and cost-effective alternative to IV penicillin for the treatment of Lyme neuroborreliosis.
Malaria			

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Weiss WR, Oloo AJ, Johnson A, et al. Daily primaquine is effective for prophylaxis against falciparum malaria in Kenya: Comparison with mefloquine, doxycycline, and chloroquine plus proguanil. J Infect Dis 1995;171(6):1569-75.	Intermittent study :91 Daily study: 169 (9-14 years)	Intermittent study: for 12 weeks, multivitamin or primaquine phosphate15 mg on Monday, Wednesday and Friday. Daily study: 11 week Daily multivitamin, daily primaquine 15 mg, daily doxycycline 50 mg, daily multivitamin plus mefloquine 125 mg or daily proguanil 200 mg plus weekly chloroquine 150 mg Daily Study: Doxycycline (32) Vitamin (34) Primaquine (32) Mefloquine (30) Chloroquine plus proguanil (37)	Primaquine was assessed in children as a prophylactic drug against *Plasmodium falciparum*. It was found that primaquine, doxycycline and mefloquine were equally effective in preventing both symptomatic and asymptomatic malarial infections, whereas chloroquine plus proguanil was the least effective. The authors concluded that primaquine was successful as a causal prophylactic regimen against falciparum malaria in children.

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Ponnampalam JT. Doxycycline in the treatment of falciparum malaria among aborigine children in West Malaysia. Trans R Soc Trop Med Hyg 1981;75(3):372-7.	9 (1-8 years)	Treatment of falciparum malaria with doxycycline in a dosage of 4 mg/kg body weight for 4 days: All patients were treated with chloroquine as recommended by WHO and followed up for a period of 28 days to observe resistance. All patients developed resistance to chloroquin and were administered single dose doxycycline 4 mg/kg. for 4 days	Doxycycline was less effective at a dose of 4 mg/kg for 4 days curing 5 patients out of 9, but cured 23 out of 26 patients when given at a dose of 4 mg/kg for 7 days. No AEs were reported except in 1 child, who had diarrhoea while on this treatment.
	26 (2 months-8 years)	Treatment of falciparum malaria with doxycycline in a dosage of 4 mg/kg body-weight for 7 days: Doxycycline 4 mg/kg for 7 days	

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Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Pang LW, Limsomwong N, Boudreau EF, et al. Doxycycline prophylaxis for falciparum malaria. Lancet 1987;1(8543):1161-4.	188 (10-15 years)	Doxycycline 100 mg daily for the patients over 40 kg body weight and Doxycycline 50 mg for the patients less than 40 kg body weight Chloroquine 225 mg weekly 95 Subjects doxycycline 93 Subjects chloroquine	In 95 subjects taking doxycycline for 597 man-weeks, there were 5 cases of falciparum malaria observed after treatment and 31 cases of falciparum malaria observed after treatment with chloroquine for 488 man-weeks. Doxycycline was more effective than chloroquine in the prevention of falciparum malaria infections (p<0.0001). The doxycycline group did not have significantly more AEs than the chloroquine group.
Cervicitis/Urethritis			
Thorpe EM Jr, Stamm WE, Hook EW 3rd, et al. Chlamydial cervicitis and urethritis: Single dose treatment compared with doxycycline for seven days in community based practises. Genitourin Med 1996;72:93-7.	597 (13-59)	Azithromycin single 1 g dose by mouth as four 250 mg capsules, in the clinic, atleast 1 hour before or 2 hours after a meal 402 Doxycycline 100-mg capsules, one capsule every 12 hours for seven days. 195	At the end of therapy, 349 (87%) azithromycin participants and 165 (85%) doxycycline participants completed the study. The clinical response for therapy during Week 1 follow-up and Week 2 follow-up improved from 61% to 86% in azithromycin-treated patients and from 60% to 83% in doxycycline-treated patients. Concomitant infections with *Neisseria gonorrhoeae* occurred in 31 azithromycin-treated patients and 15 doxycycline-treated patients. All patients in both the treatment groups were clinically cured at 1-week follow-up with a clinical failure in doxycycline-treated patients during Week 2 follow-up. The most common AEs noted in the azithromycin group were nausea (n = 66, 16%) and diarrhoea (n = 36, 9%) and in doxycycline group is nausea (n = 43; 22%). Elevated levels for liver function tests were noted in 10 azithromycin-treated patients and 2 doxycycline-treated patients.
Khosropour CM, Manhart LE, Colombara DV, et al. Suboptimal adherence to doxycycline and treatment outcomes	184 (≥16 years)	Doxycycline 100 mg twice a day for 7 days plus Placebo azithromycin single dose 92	Baseline prevalence of *Chlamydia trachomatis*, *Mycoplasma genitalium* and *Ureaplasma urealyticum-biovar-2* was 26%, 13% and 27%, respectively. Twenty-eight (28%) per cent of men reported imperfect adherence, and this was associated with microbiologic failure among men with *Chlamydia trachomatis* (aRR = 9.33; 95% CI = 1.00-89.2) and *Ureaplasma urealyticum-biovar-2* (aRR = 3.08; 95% CI = 1.31-7.26) but not

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Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
among men with non-gonococcal urethritis: A prospective cohort study. Sex Transm Infect 2014;90(1):3-7. .		Placebo doxycycline twice daily for 7 days plus Active azithromycin 1 g as a single dose (two 500-mg or four 250-mg tablets) 92	*Mycoplasma genitalium*. Imperfect adherence was not significantly associated with clinical failure overall or for any specific pathogens, but it was more common among imperfectly adherent men with CT (aRR = 2.63; 0.93-7.41, p = 0.07). In this study population, suboptimal adherence to doxycycline was significantly associated with microbiologic failure among men with *C. trachomatis* and *U. urealyticum-biovar*.
Geisler WM, Uniyal A, Lee JY, et al. N Engl J Med 2015;373(26):2512-21. To assess whether azithromycin is noninferior to doxycycline in the treatment of *Chlamydia* among youth in correctional facilities.	567 (12-21 years)	Azithromycin 1 g in a single dose 284 Doxycycline 100 mg twice a day for 7 days 283	In total, 150 out of the 201 male participants (75%) reported not having urogenital symptoms. Sixty-seven (67) out of the 109 female participants (61%) reported urogenital symptoms, most commonly abnormal vaginal discharge (54 of 109, 50%). PID was not diagnosed in any female participant. Previous *Chlamydia* infection was self-reported by 22% of the male participants (44 of 201) and was documented in 20% (40 of 201) of the patients. Female participants self-reported previous *Chlamydia* infection more often than it was documented (44 [40%] versus 32 [29%], p = 0.001). No treatment failures occurred in the doxycycline group (0%; 95% CI, 0.0-2.4). There were 5 treatment failures among participants who received azithromycin (3.2%; 95% CI, 0.4-7.4): 4 in male participants (3.9%; 95% CI, 1.1-9.7) and 1 in a female participant (1.9%; 95% CI, 0.0-10.1); all the participants with treatment failure were asymptomatic. Adverse events were reported in 23% of the participants in the azithromycin group and in 27% of the participants in the doxycycline group; the most common adverse events reported in both the groups were gastrointestinal symptoms. No severe or serious adverse events occurred, and no participants discontinued the study because of an AE.
Filaricidal Activity			

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Turner JD, Tendongfor N, Esum M, et al. Macrofilaricidal activity after doxycycline only treatment of *Onchocerca volvulus* in an area of *Loa loa* co-endemicity: A randomized controlled trial. PLoS Negl Trop Dis 2010;4(4):e660.	172 (15-60 years)	Doxycycline 200 mg/day + Ivermectin 150 μg/kg (*Onchocerca volvulus* single infection) 60 Doxycycline 200 mg/day + Ivermectin 150 μg/kg (*O. volvulus* + *L. loa* co-infection) 22 Doxycycline 200 mg/day 30 Ivermectin 150 μg/kg 60	A 6-week course of doxycycline delivers macrofilaricidal and sterilising activities, which is not dependent upon the co-administration of ivermectin. Doxycycline is well tolerated in patients co-infected with moderate intensities of *L. loa* microfilariae. The trial indicated that anti-wolbachia therapy is a feasible alternative to ivermectin in communities co-endemic for onchocerciasis and loiasis. Treatment with doxycycline was well tolerated, and the incidence of adverse event to doxycycline or ivermectin did not significantly differ between the treatment groups.
Debrah AY, Mand S, Marfo-Debrekyei Y, et al. Macrofilaricidal effect of 4 weeks of treatment with doxycycline on *Wuchereria bancrofti*. Trop Med Int Health 2007;12(12):1433-41.	25 (18-60 years)	Doxycycline 200 mg/day for 4 weeks 18 Control group 7	Four (4) months after treatment with doxycycline, a significantly lowered *Wolbachia* load was observed when compared with the control group. It was concluded that a 4-week regimen of doxycycline was sufficient to kill adult *W. bancrofti*.
Taylor MJ, Makunde WH, McGarry HF, et al. Macrofilaricidal	72 (15-68 years)	Doxycycline 200 mg/day for 8 weeks 34	Doxycycline treatment almost completely eliminated microfilaraemia at 8 to 14 months' follow-up. Adult worms were detected in 6 (22%) of 27 individuals treated with doxycycline compared with 24 (88%) of 27 with placebo at 14

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Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
activity after doxycycline treatment of *Wuchereria bancrofti*: A double-blind, randomised placebo-controlled trial. Lancet 18-24 Jun 2005;365(9477).		Placebo for 8 weeks 38	months after the start of the treatment. Filarial antigenaemia in the doxycycline group fell to about half of that before the treatment (p = 0·015). It was concluded that an 8-week course of doxycycline was found to be safe and well-tolerated treatment for lymphatic filariasis with significant activity against adult worms and microfilaraemia.
Coulibaly YI, Dembele B, Diallo AA, et al. N Engl J Med 2009;361(15):1448-58. To evaluate the efficacy of doxycycline for the treatment of *M. perstans* infection in subjects with *M. perstans* microfilaremia with or without concomitant infection with *W. bancrofti*.	216 (14-65 years)	Doxycycline (200 mg daily for 6 weeks) or no treatment Positive for both *M. perstans* and *W. bancrofti* - no treatment (N = 67), doxycycline (N = 64) Positive for *M. perstans* and negative for *W. bancrofti* - no treatment (N = 43) doxycycline (N = 42)	At 6 months, subjects who were coinfected with *W. bancrofti* underwent a second random assignment, to treatment with a single dose of albendazole (400 mg) and ivermectin (150 µg per kilogram of body weight) or no treatment. Mild adverse events like headache, diarrhoea and respiratory symptoms were reported in both doxycycline and no-treatment groups. A complete clearance of *M. perstans* microfilariae at 12 months was achieved in 67 of 69 subjects (97%), who received doxycycline only, as compared with 10 of 63 subjects (16%), who had received no treatment (relative risk, 6.18; 95% CI, 3.63 to 11.89; p<0.001) and 5 of 27 subjects (19%), who had received albendazole–ivermectin, but not doxycycline. Doxycycline was effective in reducing the *W. bancrofti* microfilariae levels.
Supali T, Djuardi Y, Pfarr KM, et al Clinical Infectious Diseases. 46(9):1385-93, 2008 May 1. The primary objective was to assess whether a 6-week course of doxycycline treatment was	161 (12–76 years)	Groups I& II- 1 capsule of doxycyline (100 mg) per day for 6 weeks; Group III-1 capsule placebo per day for 6 weeks 119 (doxycycline), 42 (Placebo)	There was a significant reduction in the microfilaria count compared with that before doxycycline treatment (for all groups p<0.001) was highest in the groups treated with doxycycline and lowest in the group treated with placebo doxycycline (89%, 83%, and 39% for the doxycycline plus placebo diethylcarbamazine-albendazole group, the doxycycline plus diethylcarbamazine-albendazole group, and the placebo doxycycline plus diethylcarbamazine-albendazole group, respectively). The prevalence of microfila emia was reduced to 77% and 87.5% in diethylcarbamazine-albendazole and the

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Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
effective in reducing Wolbachia loads in *B. malayi*–infected persons and, when given in combination with diethylcarbamazine plus albendazole, whether treatment would result in sustained amicrofilaremia in subjects with brugian filariasis Secondary objective was to reduce adverse reactions due to standard antifilaria drugs.		After 4 months, Groups II and III- single dose of diethylcarbamazine (6 mg/kg) plus albendazole (400 mg). Group I- placebo instead of diethylcarbamazine and albendazole. After 4 months 62(Placebo DEC-albendazole), 57(DEC-albendazole), 42(DEC-albendazole).	doxycycline plus diethylcarbamazine-albendazole groups. *Wolbachia* loads were reduced by 98% 4 months after beginning doxycycline treatment. The group treated with doxycycline plus diethylcarbamazine-albendazole had less proportion of high fever and severe adverse drug reactions.
Respiratory Tract Infections			
Richards JG. Curr Med Res Opin 1980;6(6):393-7. To compare the efficacy of doxycycline and amoxycillin in the treatment of respiratory tract infections requiring antibiotic therapy.	267 (>12 years)	Doxycycline 200 mg/day first day and subsequently 100 mg/day. In severe infections: 100 mg twice a day. 134 Amoxycillin 250 mg 3 times daily and for more severe infection: 500 mg 3 times daily. 133	Patients with respiratory tract infections were assessed. It was observed that both the antibiotics were equally effective in providing prompt improvement and complete resolution of the infection. Doxycycline showed better response. The difference in responses between the 2 groups was statistically significant in patients with acute and acute-on-chronic bronchitis.

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Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Casado MJ. Doxycycline in respiratory tract infections. Report of a retrospective study in Spain during the winter 1972-1973. Chemotherapy 1975;21(Suppl 1):76-90.	1653 (5-98 years)	Doxycycline 200 mg on the first day of therapy and 100 mg/day on each successive day. The paediatric dosage was 4 mg/kg on the first day and then 2 mg/kg on each successive treatment day. 1653	A very good or good response was observed in 85% of patients; 12.2% of patients had a moderate response and there were only 39 patients (2.4%) who were rated as having a negative response. The effectiveness of doxycycline did not reduce in the 7 years of study in the population. Thirty-seven (37) treatment-related AEs were observed in 31 out of the 1653 patients. Majority of the AEs included gastrointestinal disorders. Most frequent AEs were heartburn and gastritis (15 patients), vomiting (6 patients) and allergic skin symptoms (7 patients).
Pestel M. Doxycycline in the treatment of respiratory tract infections. Results of a pan-European multi-centre trial. Chemotherapy 1975;21(Suppl 1):91-108.	1747 (6 - 80 years)	200-mg doxycycline on the first day and 100 mg a day thereafter, but patients who were severely ill could be continued on 200 mg of doxycycline a day 1747	The improvement was noted to be rapid in the trial. There were 1257 patients (72%) who were noted to be improved by the 3rd day. This figure increased to 90% by the 5th day of therapy and to 95% by the 8th day. The overall response was good or very good in 87.9% of patients. The majority of patients (90.5%) did not experience any AEs. In the 9.5% who did, they were usually mild and self-limiting. Only gastrointestinal side effects were observed.
Typhus			

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Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Bhata NK, Dhar M, Mittal G, et al. Scrub typhus: A common rickettsial disease emerging in a new geographical region of north India. J Pediatr Infect dis 2014;9(2):93-9.	62 (1.5 months-18 years)	Ten (10)-day course of oral doxycycline 4 mg/kg/day taken twice a day or parenteral azithromycin 10 mg/kg/day once a day or chloramphenicol 100 mg/kg/day administered 4 times daily Doxycycline therapy in 43 patients and chloramphenicol or azithromycin therapy in 19 patients	Fifty–four (54; 87%) children became afebrile within 48 hours of initiating antibiotics, which were continued for 10 days. The median time to defervescence was 24 hours (range 12-60 hours). Four (4) children died with a mortality rate of 6.4%. All these children had multi-organ dysfunction and presented with refractory shock. Contributors to mortality in these children were myocarditis (3), ARDS (3), AKI (3), meningoencephalitis (1) and pneumonia (1).
Palanivel S, Nedunchelian K, Poovazhagi V, et al. Clinical profile of scrub typhus in children. Indian J Pediatr 2012;79(11):1459-62. .	67 (<12 years)	Doxycycline (dose not specified) 46 Azithromycin (dose not specified) 17	Fever was reported in all 67 children. Oedema of the extremities and facial puffiness were present in 52 (77.61%) and 50 (74.62%) children, respectively. Cough was present in 49 (73.13%) children. Vomiting and altered sensorium were seen in 40 (59.70%) and 39 (58.20%) children, respectively. Hepatomegaly, splenomegaly and pallor were the major clinical findings encountered in 66 (98.50%), 59 (88.05%) and 56 (83.58%) children, respectively. Forty (40; 59.70%) children had lymphadenopathy and 31 (46.26%) children had eschar. Eschar was found in the skin folds of axilla, genitalia and inguinal area, etc. Out of 67 children, 8 children died with mortality rate of 11.94%. All these children were presented with refractory shock. Other contributors for mortality were MODS (62.5%), ARF (50%), ARDS (37%) and DIVC (12.5%).

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Chanta C, Chanta S. Clinical study of 20 children with scrub typhus at Chiang Rai Regional Hospital. J Med Assoc Thai 2005;88(12):1867-72.	20 (age not specified)	Not available Not available	The most common clinical feature was eschar (75%). Others included hepatomegaly (65%), cough (60%), lymphadenopathy (40%), tachypnoea (35%), constipation (25%), abdominal pain (20%), oedema (20%), splenomegaly (15%), vomiting (15%), rash (15%) and petechia (5%). Elevated levels of SGOT and SGPT were detected in 18 (90%) and 15 (75%) cases. Hypoalbuminaemia was detected in 12 (60%) cases. The Weil-Felix test was positive in 1 (5%) case. Complications reported were pneumonia with or without pulmonary oedema, meningitis and shock. Treatment with chloramphenicol and doxycycline were successful, whereas roxithromycin treatment was not effective.
Perine PL, Krause DW, Awoke S, et al. Single-dose doxycycline treatment of louse-borne relapsing fever and epidemic typhus. Lancet 1974; 2:742–744.	39	Single oral dose of 100 mg of doxycycline 36	Twenty-six (26) patients with louse-borne relapsing fever and 10 patients with serologically proven epidemic typhus were treated with a single oral dose of 100 mg of doxycycline. All patients were cured and no relapses of LBRF or typhus occurred during the 2-week period of post-treatment observation. No AEs of doxycycline were observed.
Lymphatic Malformations			
Chaudry G, Burrows PE, Padua HM, et al. J Vasc Interv Radiol 2011;22(10):1431-5. To assess the safety and efficacy of percutaneous image-guided sclerotherapy with doxycycline as primary treatment of intraabdominal lymphatic malformations (LMs).	10 (2-28 years)	Doxycycline 10 mg/mL, per-session dose of 608 mg (range 80-1000 mg) and a mean total dose of 1230 mg (range 80-3000 mg) 10	Preprocedural cross-sectional imaging demonstrated a macrocystic malformation in 9 patients and a mixed macrocystic/microcystic malformation in 1 patient. In 8 patients, drainage catheter was placed through which sclerotherapy was repeated. Doxycycline was reconstituted at a dose of 10 mg/mL. Peritoneal spill was identified in 1 case, but the patient remained asymptomatic. Response to sclerotherapy was classified as complete if greater than 90% of the lesion had resolved based on imaging criteria and partial if the lesion had decreased in size by 25%–90%. Seven (7) patients showed complete resolution and 1 with partial resolution. Eight (8) patients were available for follow up and no recurrence was observed.

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Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Cahill AM, Nijs E, Ballah D, et al. J Pediatr Surg 2011;46(11):2083-95. To evaluate the clinical outcomes of percutaneous sclerotherapy for congenital head and neck lymphatic malformations (LMs).	17 children (5 days to 13 months)	10 mg/mL doxycycline through catheter in 3 instillations with a dose range of 50 to 500 mg per session on a routine basis to all 17 subjects. Additional treatments (direct injection doxycycline, instillation of absolute ethanol or sodium tetradecyl sulphate or a combination of these methods). 17 10/17 for direct injection doxycycline, 7/17 instillation of absolute ethanol, 4/17 sodium tetradecyl sulfate, or a combination of these methods.	Children who underwent 49 sclerotherapy procedures for congenital head and neck malformations were studied. An imaging improvement of >76% was noted in 11 of 17 subjects. Four (4) subjects had 51% to 75% resolution and 2 subjects had 25% to 50% resolution with a mixed lesion. Neonates prone to systemic complications (haemolytic anaemia, hypoglycaemic, metabolic acidosis, transient hypotension, and self-limiting skin excoriation) were treated with doxycycline doses of greater than 250 mg, which resulted in serum levels of >5 μg/mL, but as high as 21 μg/mL. Catheter-directed doxycycline sclerotherapy provided excellent results for large macrocystic head and neck lymphatic malformations

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Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Burrows PE, Mitri RK, Alomari A, et al. Percutaneous sclerotherapy of lymphatic malformations with doxycycline. Lymphat Res Biol 2008;6(3-4):209-16.	41 (3 months-31 years).	Doxycycline 10 mg/mL injected to fill the lesion under sonographic or fluoroscopic guidance 41	Medical records of all patients with LMs, who underwent sclerotherapy with doxycycline between 01 January 2003 and 01 September 2004 were reviewed. Follow-up imaging was performed to assess for change in lesion size. Sixty (60) sclerotherapy procedures were performed on 41 patients in the 20-month study period. The mean outcome score by imaging was 4.41/5 with a 95% CI of [4.13-4.68], which corresponded to about an 83% reduction in lesion size. Higher complication rates were seen associated with microcystic and combined lesions ($p = 0.03$), and greater doxycycline dose ($p = 0.05$). The authors concluded that doxycycline is a safe and effective sclerosant for LMs.
Leptospirosis			
Phimda K, Hoontrakul S, Suttinont C, et al. Antimicrob Agents Chemother 2007;51(9):3259-63. Multicentre, open-label, randomised-controlled trial to compare the efficacies and tolerabilities of doxycycline and azithromycin for the treatment of acute undifferentiated fever with suspicion of either Leptospirosis or scrub typhus in areas of high leptospirosis and scrub typhus endemicity.	296 (15-88 years)	Oral doxycycline (Siam Pharmaceutical) (200 mg first dose, followed by 100 mg every 12 hours for 7 days) 145 Patients in doxycycline (median age 38 [15-79] years) A 3-day course of azithromycin (Pfizer International) (1 g initially, followed by 500 mg once daily for 2 days). 151 Patients in azithromycin group (median age 38 [15-88] years)	The cause of acute fever was determined for 151 out of 296 patients (51%). In the doxycycline group, 3 patients experienced treatment failure and 4 patients in azithromycin group ($p = 0.12$). In addition, 2 patients with unknown diagnosis were discontinued due to severe AEs (may be rash or severe vomiting occurred in each) in doxycycline group. The cure rate of azithromycin was non-inferior to that of doxycycline: 96.5% in the doxycycline group and 97.4% in azithromycin group, with a difference of 0.9% (90% confidence interval, -4.6% and 2.8%). Within 5 days after initiation of treatment, doxycycline-treated patients became afebrile. Doxycycline is contraindicated in children under 8 years or during pregnancy where azithromycin is an alternative. Azithromycin was better tolerated than doxycycline, but it is more expensive (approximately $10 versus $2 per treatment course) and less readily available.

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Suputtamongkol Y, Niwattayakul K, Suttinont C, et al. An open, randomized, controlled trial of penicillin, doxycycline, and cefotaxime for patients with severe leptospirosis. Clin Infect Dis 2004;39(10):1417-24.	540 (13-92 years)	Penicillin G sodium (1.5 million U IV/6 hours) 181 Patients in penicillin G sodium group Doxycycline (200 mg infused for 30 minutes, followed by infusion of 100 mg/12 hours) 172 Patients in doxycycline group Cefotaxime (1 g IV/6 hours) 187 Patients in cefotaxime group	Patients with severe leptospirosis were assessed. It was observed that death and clinical treatment failure, duration of fever, and duration of organ dysfunction after treatment were similar among the 3 treatment groups. Two hundred and sixty-four (264) patients had leptospirosis confirmed by serologic testing or culture, and overall mortality rate was 5%. A total of 132 patients had rickettsial infection diagnosed, and for these patients, treatment with penicillin G was significantly less effective than doxycycline or cefotaxim. The authors concluded that doxycycline or cefotaxime is a satisfactory alternative to penicillin G for the treatment of severe leptospirosis.
Rickettsial Infections			
Alvarez-Hernandez G, Murillo-Benitez C, Candia-Plata Mdel C, et al. Pediatr Infect Dis J 2015;34(2):125-30. To characterise clinical features and predictors of death in hospitalised paediatric RMSF cases, in order to provide general clinical guidance for preventing fatal outcomes.	104 (0 months-19 years)	Doxycycline IV 82 Oral Doxycycline 17 Chloramphenicol 2 Oxytetracycline 2 None1	The overall case fatality rate (CFR) was 20% for the entire study period. The highest CFR (24%; 18 deaths) occurred in children aged below 10 years, compared with older children (10%; 3 deaths), although no statistical difference was observed (p = 0.264). The mean time from presentation to death was 9.8 ± 1.7 days. Non-fatal cases were hospitalised for a mean of 16.2 ± 9.0 days. The mortality rate (91%) among those patients for whom doxycycline was initiated on Day 5 or later from onset was significantly higher than those for whom doxycycline was initiated on Day 4 or earlier (10%), and the relative risk of mortality for delay in treatment was 3.01, (CI 95%: 1.18-14.63). Doxycycline was the elected treatment in 95% of the patients, an identical proportion for both the groups; the drug treatment was initiated later after onset in 85% of patients in the fatal group, in contrast to 71% in the non-fatal group (p = 0.262).
Yagupsky P, Gross EM, Alkan M, et al. Comparison of two dosage schedules of doxycycline in children with rickettsial spotted	50 (4 months-156 months [13 years])	Doxycycline 4.4 mg/kg twice a day on first day and 2.2 mg/kg twice a day for 7 days (STG) 25	Patients in the CTG who did not relapse became afebrile within one to five days. These patients were treated for an average of 3.9 days, and their treatment time ranged from 2 to 6 days. Patients in the STG became afebrile within one to six days. None of the differences in means were statistically significant (p< .05). No serious complications occurred, and no adverse reactions to treatment

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
fever. J Infect Dis 1987;155(6):1215-9.		Doxycycline 4.4 mg/kg twice a day on first day and 2.2 mg/kg twice a day till patient is afebrile for 24 hours (CTG) 25	were noted. Only 1 patient in the CTG had a recurrence of fever 24 hour after discontinuing therapy. This patient subsequently received doxycycline for 1 week and recovered uneventfully. All the others in the CTG had uneventful courses and completed treatment in 6 days or less. Results of this study indicate that administration of oral doxycycline until paediatric patients with uncomplicated ISF become afebrile and continuing treatment for 24 hours is as effective as 1 week's therapy.
Nawab T, Srinivassa S, Reddy SP. Curr Pediatr Res 2015;19(1-2):17-20. To identify the clinical features, complications and outcome of rickettsial infections in children.	30 (<18 years)	Doxycycline 30	Scrub typhus was diagnosed in 14 (46.7%), spotted fever in 8 (26.7%), typhus in 2 (6.7%) and remaining 6 (20%) showed mixed features. School-going children were commonly affected. In 25 cases (83.3%), rashes were observed and were more prominent in febrile patients. Other clinical features included vomiting in 11 cases (36.7%), pain abdomen in 8 (26.7%), diarrhoea in 3 (10%), constipation and jaundice in one case each (3.3%). Examination revealed hepatomegaly in 14 cases (46.7%), conjunctival congestion in 10 (33.3%), associated splenomegaly in 7 (23.3%), pedal edema in 7 (23.3%), lymphadenopathy in 1 case (3.3%). All patients recovered with doxycycline therapy.
Meloni G, Meloni T. Azithromycin vs doxycycline for Mediterranean spotted-fever. Pediatr Infect Dis J 1996;15:1042-4.	30 (2-11 years)	Doxycycline 5 mg/kg/day for 5 consecutive days 15 Azithromycin 10 mg/kg/day for 3 consecutive days 15	No statistically significant difference was observed with regard to the mean of the peak daily temperature between the 2 treatment groups. Regarding the other symptoms (maculopapular exanthema, headache, generalised arthromyalgias, tache noire; hepatosplenomegaly and lymphadenopathy) a gradual resolution was observed in all patients after the second day of treatment, without a clinically appreciable difference between the 2 treatment groups. Azithromycin and doxycycline were equally well-tolerated by the patients; none of the 30 treated children presented signs or symptoms attributable to the administration of the antibiotics. All the patients attended follow-up examinations at 15-day intervals for 30 days after discontinuation of antibiotics. None showed clinical signs or symptoms consistent with a recurrence of MSF.
Aneurysmal Bone Cysts			

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Shiels W, Murakami J. Directed tumoral therapy of aneurysmal bone cysts in children. Pediatr Radiol 2011;41(Suppl):S283. To evaluate clinical.	38 (2-18 years)	Doxycycline microfoam (10 mg/mL; percutaneous administration) into cystic and solid tumoural elements with US, CT or fluoroscopic-directed guidance (mean dose = 300 mg/session) 38	Children were assessed to evaluate clinical feasibility and efficacy of doxycycline as a multimodal (antitumoural, MMP inhibition and osteoblastic stimulation) antineoplastic therapy. Bony healing of lytic foci, with stability during surveillance was followed-up to 2 to 48 months. It was observed that doxycycline microfoam was visible with US in 92 cases targeting solid tumoural elements followed by bony-healing response (34/34 patients) and biopsy-proven antitumoural response in 4 cases. The authors concluded that directed antitumoural therapy with doxycycline microfoam is feasible, safe and effective for percutaneous treatment of ABC in the axial and appendicular skeleton of children.
Shiels WE, Beebe AC, Mayerson JL. J Pediatr Orthop 2016;36(2):205-12. Retrospective review of 16 patients, who underwent percutaneous treatment of ABCs with doxycycline from 2006 to 2011.	16 Patients (2 to 15 years) who underwent percutaneous treatment of ABCs with doxycycline	102 Treatment sessions (2 to 14 sessions per patient) 16	Sixteen (16) patients who underwent percutaneous treatment of ABCs with doxycycline were reviewed. A reduction in lytic destruction, bone healing and bone remodelling were observed in all the 16 patients and recurrent minimal lytic destruction after 20 months of observation was demonstrated by 1 patient. Focal bone bridge was demonstrated by all the patients with focal transphyseal ABC involvement. Seven (7) patients demonstrated physeal ABC involvement and only patients with intraphyseal or transphyseal ABC involvement had focal physeal growth arrest. Healing and a recurrence rate of 6% at >18 months was observed in patients undergoing percutaneous doxycycline treatment of juxtaphyseal ABCs and patients without physeal ABC involvement demonstrated no evidence of physeal growth arrest.
Pelvic Inflammatory Disease			
Gjonnaess H, Holten E. Acta Obstet Gynecol Scand 1978;57(2):137-9. Role of doxycycline in the treatment of pelvic inflammatory disease.	85 (16-45 years)	200 mg of Doxycycline followed by 100 mg daily dose 85	Patients were assessed for the role of doxycycline in the treatment of PID. Fluid aspirated from the pouch of Douglas, the Fallopian tubes and ovarian cysts were measured for the concentration of doxycycline after the oral ingestion of 200 mg of doxycycline. Within a few hours of drug administration, it was observed that a therapeutic level was achieved in the tubes and in ovarian cysts, and the clinical effect was excellent having 94% (60/64) of the cases with verified PID being cured by doxycycline.
Trachoma			

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Darougar S, Jones BR, Viswalingam N, et al. Br J Ophthalmol 1980;64(4):291-5. To assess the efficacy of family-based intermittent therapy of hyperendemic trachoma with topical oxytetracycline or oral doxycycline in comparison with a control group.	129 (0 months-11 years)	One per cent (1%) oxytetracycline oily suspension twice a day for 7 days every month for 12 months 38	Patients with active trachoma in their whole conjunctiva were assessed. No marked difference in the cure rate or the number of patients with moderate-to-severe trachoma between the groups treated with antibiotics and the control group was observed. But a marked decrease in the prevalence of trachoma and in the grades of intensity of inflammatory responses as well as the positivity rate for *Chlamydia trachomatis* were observed in the topical oxytetracycline group and oral doxycycline group.
		Oral doxycycline 5 mg/kg body weight once a month for 12 months 44	
		Vitamin pills for the control group 47	
Hoshiwara I, Ostler HB, Hanna L, et al. JAMA 1973;224(2):220-3. To evaluate the efficacy of doxycycline in the treatment of chronic trachoma	120 (7-13 years)	Doxycycline, 2.5 to 4 mg/kg of body weight, given as a single daily dose on five days each week, for a total of 28 doses given in 40 days Placebo 49 Doxycycline group 54 Placebo group	Detailed ophthalmologic evaluation continued for five months after the treatment course. The trachoma in the doxycycline-treated children improved markedly, as compared to those receiving placebo ($p<0.001$ at 20 weeks after treatment). Based on the results the authors stated that a single daily dose of doxycycline given 28 times in 40 days effectively suppressed the signs of active trachoma for at least 20 weeks.
Sinusitis			

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Herz G, Gfeller J. Chemotherapy 1977;23(1):50-7. To assess the result of treatment of sinusitis in childhood with the antibiotic, doxycycline.	106 (6-17 years)	Doxycycline was given in the recommended doses: 4 mg/kg on the first day, followed by 2 mg/kg daily thereafter. The dose in the patients aged from 14 to 17 years was 200 mg on the first day, followed by 100 mg daily thereafter. 106 (17 patients are of age 14-17 years)	A successful result was obtained in 94.3% of cases; cure in 77 patients (72.6%) and marked improvement in 23 (21.7%). There were 6 failures (5.7%). In most children—72 cases (68%), the duration of treatment was 15 to 21 days. It was 10 to 14 days in 18 children (17%) and more than 3 weeks in 16 children (15%). Rapid subjective improvement was seen in 65 cases (61.3%), and rapid objective improvement in 80 (75.5%). The tolerance of doxycycline was very good in nearly all the patients. Mild symptoms of gastrointestinal intolerance were observed in 2 cases.
Pneumonia			

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Lung DC, Yip EK, Lam DS, et al. Rapid defervescence after doxycycline treatment of macrolide-resistant *Mycoplasma pneumoniae*-associated community-acquired pneumonia in children. Pediatr Infect Dis J 2013;32(12):1396-9. .	208 (<18 years)	Doxycycline 4 mg/kg/day for the first day, followed by 2 mg/kg/day for 9 days; for severe cases, doxycycline at the dosage of 4 mg/kg/day for 10 days or levofloxacin 5 mg/kg/day for 10 days 208	All 34 patients infected with MRMP received β-lactam plus macrolide as the initial therapy on admission. Sixteen (47.05%) patients switched to doxycycline from macrolide after molecular results were available whereas 18 patients within the MRMP group continued to receive macrolide treatment throughout the period of hospitalisation despite the molecular result showed resistance toward macrolide. Only 1 patient (5.56%) who received macrolide alone achieved defervescence within 24 hours and mean TTD for macrolide was 123.33 ± 59.05 hours. All patients who received doxycycline therapy achieved defervescence within 24 hours and the mean TTD was 13.50 ±4.10 hours, which was significantly shorter than the TTD for group of patients who received macrolide ($p = 0.0001$). The mean TTD for patients with MSMP who received macrolide was 80±39.80 hours, although slightly shorter than the MRMP group, it was not statistically significant ($p = 0.0862$). Three patients in the MSMP group received doxycycline and the mean TTD was 16±6.90 hours. Doxycycline was significantly more effective than macrolide for the treatment of MRMP-associated community-acquired pneumonia in terms of achievement of rapid defervescence within 24 hours.
Okada T, Morozumi M, Tajima T, et al. Rapid effectiveness of minocycline or doxycycline against macrolide-resistant *Mycoplasma pneumoniae* infection in a 2011 outbreak among Japanese children. Clin Infect Dis. 2012 Dec;55(12):1642-9.	202 (<15 years)	Doxycycline 4 mg/kg/day twice daily or Minocycline 4 mg/kg/day twice daily 141 Tosufloxacin 12 mg/kg/day twice daily 17	Among 202 *M. pneumoniae* isolates from *M. pneumoniae*–associated pneumonia patients, 176 (87.1%) were MRMP. Macrolide-resistant *M. pneumoniae* infection was significantly related to school age ($p<.01$) and initial administration of macrolides ($p<.01$). Minocycline or doxycycline (n=125) or tosufloxacin or levofloxacin (n=15) was used for definitive treatment of MRMP patients. Minocycline or doxycycline was significantly more effective than tosufloxacin ($p\leq.05$) in achieving defervescence within 24 hours and in decreasing numbers of *M. pneumoniae* DNA copies 3 days after initiation. When minocycline or doxycycline was administered, almost 90% of patients showed defervescence and other improvements in clinical findings within 48 hours.
Plague			

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Mwengee W, Butler T, Mgema S, et al. Treatment of plague with gentamicin or doxycycline in a randomized clinical trial in Tanzania. Clin Infect Dis 2006;42(5):614-21. .	65 (0.6 to 65 years)	Gentamicin 2.5 mg/kg doses IM Gentamicin recipients (n = 35) Median age 11 (0.6-6.5) Doxycycline 100 mg capsules for adults. For children, powder from capsules suspended in 100 mL of water in 2.2-mg/kg doses Doxycycline recipients (n = 30)	One (1) patient treated with doxycycline and 2 treated with gentamicin died because of pneumonia, septicaemia, haemorrhage and renal failure at the start of therapy. Favourable response rates were observed 94% for gentamicin (95% CI, 81.1%–99.0%) and 97% for doxycycline (95% CI, 83.4%–99.8%). The estimated difference of response rates (gentamicin-doxycycline) was -3% (95% CI for true difference in response rates, -16.1% to 12.1%; p>0.05). When patients returned for follow-up visits 1–2 weeks after the end of therapy, no relapses had occurred. Four (4) patients failed to return for follow-up visits; 3 of these had received gentamicin, and 1 had received doxycycline. Patients treated with gentamicin demonstrated a modest increase in the mean serum creatinine concentration after treatment (p<0.05, by paired t-test).
Morel-Lavallee Lesions			
Bansal A, Bhatia N, Singh A, et al. Doxycycline sclerodesis as a treatment option for persistent Morel-Lavallee lesions. Injury 2013;44(1):66-9.	16 (10-74 years)	Doxycycline 500 mg in 25-mL saline 16	The average duration of the persistence of the lesion was 13 months (range, 6-23 months). All the lesions were aspirated and found to be negative on culture. Eleven (11) patients showed complete resolution of fluid collection at 4 weeks with another 4 patients resolving at 8 weeks' follow-up. The lesion persisted in 1 patient at 12 weeks due to non-compliance to compressive elastic bandaging, which subsequently resolved on repeating the procedure. All the lesions healed without any infections or necrosis. No recurrences were detected during the follow-up period. A persistent non-fluctuant contour deformity, decreased skin mobility over the site of lesion and feeling of tightness were the most common problems faced on long-term follow-up.
Cholera			

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Alam AN, Alam NH, Ahmed T, et al Randomised double blind trial of single dose doxycycline for treating cholera in adults. BMJ. 1990 Jun 23;300(6740):1619-21.	246 (12-60 years)	Doxycycline 200 mg 82 Doxycycline 300 mg 80 Tetracycline 500 mg with 6 hours interval 84	The median stool outputs during the first 24 hours (275 mL/kg body weight) and till diarrhea stopped (296 mL/kg body weight) were significantly higher in patients receiving 200 mg doxycycline as a single dose than in patients receiving either standard tetracycline (242 mL/kg body weight and 254 mL/kg body weight) or 300 mg doxycycline (226 mL/kg body weight and 255 mL/kg body weight). Similarly, median consumption of oral rehydration solution (18.45L) was significantly higher in patients receiving 200 mg doxycycline than in patients receiving either 300 mg doxycycline (16.10L) or standard tetracycline (14.80L). Almost equal numbers of patients in each group required unscheduled intravenous acetate solution to correct dehydration during antibiotic treatment. Patients treated with doxycycline (low or high dose), however, had more prolonged excretion of bacteria. Based on the results the authors concluded that a single 300 mg dose of doxycycline was as effective as the standard multiple dose tetracycline treatment for cholera.
Others			
Herz G, Gfeller J. Vibramycin in paediatrics. An evaluation of the onset of action and efficacy. Chemotherapy 1975;21 (Suppl 1):58-67.	246 (5-18 years)	Doxycycline was administered at the recommended dosage of 4 mg/kg body weight on the first day, and 2 mg/kg body weight on each successive day. The daily dosage administered to children aged 14 to 18 years was 200 mg on the first day and 100 mg daily thereafter. 246	The infection studied in this study were Bronchopneumonia, bronchitis (77); sinusitis, maxillary, ethmoidal (80); purulent or catarrhal otitis media, mastoiditis (72); follicular or acute tonsillitis, pharyngitis, laryngitis, purulent rhinitis, incipient tonsillar abscess (135); inguinal lymphadentitis, cervical abscess (4); furunculosis (5) and various such as pertussis, varicella, etc. (4). All patients were assessed for the subjective and objective improvement after the treatment with doxycycline, where it was found to be effective, whereas cure was obtained in 168 patients (68.6%) and marked improvement was seen in 59 (24.1%), having an overall success rate of 92.7%. Rapid subjective improvement was seen in 48 out of 58 patients (84.2%) and rapid objective improvement in 41 patients (70.7%). Tolerance to doxycycline was observed to be good. The authors concluded that doxycycline was a very suitable antibiotic for use in day-to-day paediatric practice.

Table 5: Summary of Literature Articles

Article Objective(s)	Total Patients (Age Range)	Treatment Regimen Total Number of Patients Per Regimen	Summary of Results
Volovitz B, Shkap R, Amir J, et al. Clin Pediatr (Phila) 2007;46(2):121-6. To conduct a blind, randomised, controlled clinical study comparing tooth colour and staining in doxycycline-treated and -untreated asthmatic children.	61 (8-16 years)	Doxycycline administered in syrup form (Pfizer) 4 mg/kg twice a day on the first day followed by a single dose of 2 mg/kg/day for 9 days. 31	Thirty-one (31) children had received doxycycline before the age of 8 years. Majority of the children receiving doxycycline were aged below 4 years. The parents reported that doxycycline was very effective in controlling asthma/pneumonia symptoms in 26 of the 29 children (90%) for whom data were available. In 2 children (7%), the treatment was partially effective, and in 1 child (3%), doxycycline was not effective. Six (6) out of 25 children in the doxycycline group and 5 out of 30 in the control group were classified as having poor oral hygiene (p = 0.5). White staining of the teeth, not related to doxycycline, was observed in both the groups: 11 out of 25 children treated with doxycycline and in 10 out of 30 untreated children (p = 0.58). Grade of tooth colour was bright (Grade 3-5/16) in 7 of 25 children in the doxycycline group and 6 of 30 children in the control group (p = 0.53), with no difference between children treated with doxycycline before or after the age of 4 years. None of the children had unusually coloured or significantly dark teeth (Grade 12-16/16).
Todd SR, Dahlgren FS, Traeger MS, et al. No visible dental staining in children treated with doxycycline for suspected Rocky Mountain Spotted Fever. J Pediatr 2015;166(5):1246-51.	335 (8 and 16 years)	Doxycycline 335 children	Only 58 children received doxycycline during the period of calcification of at least 1 tooth and had at least 1 of these exposed teeth fully erupted at the time of the dental examination and received 107 courses of doxycycline before 8 years of age. The mean doxycycline dose was 2.3 mg/kg (range 0.3-2.9, SD = 0.40), which is not dissimilar from the recommended dose of 2.2 mg/kg/dose (maximum, 100 mg/dose). The average age of doxycycline administration was 4.5 years old (range 0.2-7.9, SD = 2.4). No child in the study including 58 children who received doxycycline before 8 years of age (95% CI 0%-5%) developed tetracycline-like staining patterns, 10 children (4%) experienced enamel hypoplasia (p = 1.0), fluorosis-like hypomineralisation (p = 0.35) was observed in 33 children (12%), but not because of exposure to doxycycline.

ABC = aneurysmal bone cyst; AE = adverse event; AKI = acute kidney injury; ARDS = acute respiratory distress syndrome; ARF = acute renal failure; BBB = blood brain barrier; CFR = case fatality rate; CI = confidence interval; CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; CTG = curtailed-treatment group; DEC = diethylcarbamazine; DIVC = disseminated intravascular coagulation; DNA = deoxyribonucleic acid; FDS = filarial dance sign; IV = intravenous; IM = intramuscular; ISF = Israel spotted fever; LBRF = louse borne relapsing fever;LM = Lymphatic malformations; MMP = matrix metalloproteinase; MODS = multiorgan dysfunction syndrome; MR = modified release; MRMP = macrolide-resistant *Mycoplasma pneumoniae*; MSF = Mediterranean spotted fever; MSMP = macrolide-sensitive *Mycoplasma pneumoniae*; PcG = pencillin G; PNS = peripheral nervous system; PID = pelvic inflammatory disease; RMSF = Rocky Mountain Spotted Fever; SD = standard deviation; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; SGT = standard treatment group; TTD = time-to-defervescence; US = ultrasound; WHO = World Health Organisation.

Most of the articles dealt with the use of doxycycline to treat children in approved indications: acne, chlamydial infections, respiratory tract infections, Lyme disease, plague, Rocky Mountain spotted fever (RMSF), leptospirosis, scrub typhus, malaria.

Twenty-three (23) published studies included active comparators. In addition, new information regarding the use of doxycycline for the treatment of paediatric patients with lymphatic malformations and *Mansonella perstans* infection was identified. However, these studies were conducted in developing countries, most of which were in the African continent for *Mansonella perstans*. Furthermore, very limited information was available on the sclerotherapy using doxycycline in patients with lymphatic malformations. Most of the studies were pilot or preliminary trials that enrolled a few subjects, or were otherwise insufficiently robust to support a change to the label. It was therefore concluded that the MAH could not use this information to provide any paediatric specific text for addition to the doxycycline SmPC.

The MAH concluded that the published articles provided no new information regarding either the clinical efficacy or safety profile of doxycycline in children.

Rapporteur's comments:

Of the 52 published studies, 20 were paediatric studies and enrolled neonates and children up to the age of 18 years. Conditions studied included rickettsial diseases (7), sclerotherapy (4), malaria (3) trachoma (2), mycoplasma infection (2), sinusitis (1) and Lyme disease (1). At least twelve of the studies enrolled children younger than 8 years old for indications such as sclerotherapy, rickettsial disease, trachoma and malaria.

Twelve were comparator trials where doxycycline was shown to be superior to placebo and as effective or superior to other established treatments. No new paediatric safety signals were reported.

In the studies that contained a mix of adult and paediatric patients, separate analyses of paediatric safety and efficacy data were not done. Although paediatric numbers for younger ages were clarified in most of the studies, stratification of older paediatric age groups was less clear and such patients were often grouped with young adults, making further analysis difficult.

There is no new safety signal observed or described in adults or children. The side effects described are similar to those currently documented in the SmPC with no change in frequency or severity observed. There is little documented evidence of tooth discoloration however, it is noted that most paediatric patients studied were over 12 years old. In the studies that included use in children less than 12 years of age, the follow up period might have been too short to capture this adverse event.

Doxycycline was used as an intra-lesion sclerosant in 6 studies with variable dosing regimens described. These studies enrolled neonates and children up to the age of 18 years. Only a few of the 6 studies had results for plasma doxycycline levels following its use as a sclerosant. The range of levels reported were variable and above the therapeutic levels required for doxycycline's antibacterial activity. These studies were non-comparator in design and were either retrospective or case series reports. Although there are some data on efficacy, the presented evidence is deemed insufficient to warrant addition of this indication to the SmPC.

It is also noted that acute systemic adverse reactions (such as hypotension, vomiting, skin reactions) are reported in the studies for sclerotherapy, but there are no medium or long term

data on doxycycline's effects on dentition, which is a concern in the youngest age group studied.

Regarding teeth staining, two published studies were assessed:
One comparative study by Volovitz et al 2007, enrolled patients treated for refractive atypical pneumonia before the age of 8 years. There were 61 children enrolled, 30 who were treated with non-tetracycline antibiotics and 31 children treated with doxycycline (mean 4.1 years; range: 2 to 7.7 years). The mean duration of follow up was 6.3 years (+/- 2 years) from the time of first administration of doxycycline to the time of dental assessment. There was no tooth staining detected in the doxycycline-treated children compared to the non-tetracycline treatment group.

Todd et al 2015, was a retrospective study of 335 children. This comprised a control group of 213 children who never received doxycycline, 76 children who received at least 1 dose of doxycycline for the treatment of Rocky Mountain Spotted Fever prior to the age of 8 years and 46 children who were excluded from further analysis. Only 58 of the 76 children received doxycycline during the period of calcification of at least 1 tooth and had at least 1 of these exposed teeth fully erupted at the time of the dental examination. As such, these (58) were defined as the doxycycline exposed group for analysis. This exposed group received an average of 1.8 courses of doxycycline before the age of 8 years of age, at a mean age of 4.5 years (range: 0.2 to 7.9 years) for a mean duration of 7.3 days (range: 1 to 10 days). The mean age at time of dental exam of those who received doxycycline was 9.8 years. There was no difference seen in dental staining, enamel hypoplasia, or tooth colour compared with the control group.

There are a few limitations to the Todd 2015 study due to the retrospective design. Since tooth staining is considered a rare outcome, the sample size may not have been large enough to uncover the true trends of this adverse event. There is also reliance on previous medical records which may not accurately capture the duration and exposure of children to doxycycline. Despite these limitations, the published data provide updated information on doxycycline's safety profile and provide reassurance on the risk of tooth staining in children.

In published literature, dental staining is variable, reported in 23%-92% of children treated with older tetracyclines. However, when the data regarding visible dental staining from the Todd 2015 study are combined with the findings from Volovitz 2007 study, the combined dental staining rate for doxycycline is 0% (0/89 of paediatric patients exposed to doxycycline).

Safety:

The MAH submitted data from their safety database. A cumulative search of the post-marketing safety database was conducted up to 24 March 2016 to identify adverse events (AE) reports following the use of doxycycline in children (defined as patient's age having been reported as less than 18 years, or the patient described as a new-born, neonate, infant, child, adolescent or teenager by the reporter).

A total of 442 paediatric cases were identified, representing 6.03% (n = 7331) of all doxycycline AE reports in the MAH's post-marketing safety database. Of the 442 paediatric reports, 197 were classified as serious and 245 were classified as non-serious. Case outcomes were reported as fatal in 4 cases, recovered/resolved in 93 cases, recovered/resolved with sequelae in 1 case, recovering/resolving in 30 cases, not recovered/not resolved in 36 cases and unknown in 278 cases. Of the 4 fatal cases, one was possibly drug-related (anaphylaxis following IV doxycycline administration).

The System Organ Classes (SOCs) containing the greatest number of AEs included Gastrointestinal disorders (159) and Skin and subcutaneous tissue disorders (145). The most frequently reported events irrespective of SOC were Vomiting (30), Photosensitivity reaction (24), Oesophageal ulcer (22), Tooth discolouration (17) and Rash (16). The MAH concluded that no new safety concerns have been identified during the safety database review. Doxycycline cases in the MAH's safety database are reviewed quarterly and any signals identified in the paediatric population will be evaluated for possible addition to the Core Data Sheet (CDS).

Rapporteur's comments:

Doxycycline's adverse events in children represent a small proportion of all reports in the MAH's safety database and this could reflect the lower usage in the paediatric population compared to adults. Most the cases were related to doxycycline's gastrointestinal side effects or photosensitivity and are comparable to those reported in published literature. Of note, there are 17 paediatric cases of tooth staining reported, although it is not known how the cases are stratified by age group or whether the discoloration was considered permanent or temporary. Overall, the MAH's safety database review did not reveal any new safety concerns which may affect the paediatric benefit: risk profile of doxycycline.

Permanent dental discolouration is affected by the dose and duration of tetracycline treatment as well as the stage of tooth development. Tetracyclines are irreversibly bound by chelation to free calcium in developing tooth structures to form tetracycline-calcium orthophosphate complexes. These complexes darken on light exposure to form the yellow brown discolouration associated with tetracycline staining and are classified by the extent, degree and location. The risk of permanent staining is highest during in the second or third trimesters of pregnancy, (whereas the risk of bone incorporation occurs earlier). Staining is also a risk during the first 8 years of life when calcification of the permanent dentition occurs. The third molars (wisdom teeth) calcify later and thus can be exposed to the effects of tetracycline staining at a later age.

Reversible discoloration of permanent dentition in adolescents and adults have also been reported (Ayaslioglu, E., et al 2005). In these cases, staining is dependent on the dose and duration of tetracycline treatment. Although this mechanism of staining is not fully understood, it is thought to be multifactorial. The interaction of tetracyclines with components of outer tooth enamel, as well as the effects of oxidative breakdown, oral pH and metabolism by certain oral bacteria result in production of degradation compounds which darken on exposure to light and which can temporarily stain teeth. Although bone deposition of tetracyclines has been reported and is dependent on the duration of treatment (particularly with minocycline), the long-term effect on bone function and development is not known.

When compared to older tetracyclines, doxycycline has a lower potential to permanently discolour permanent teeth and deposit in bone due to its lower affinity for calcium chelation.

Ayaslioglu, E., et al. "Doxycycline-Induced Staining of Permanent Adult Dentition." Australian Dental Journal, vol. 50, no. 4, 2005, pp. 273-5, Hospital Premium Collection, https://search.proquest.com/docview/207218600?accountid=145343, doi:http://dx.doi.org/10.2264/0045-0421.50.4.1429.

3. Discussion on clinical aspects and conclusion

The results presented from the MAH's sponsored studies indicate that doxycycline is as effective as the comparators chosen for these studies in the relevant indications. While efficacy and safety were not specifically reported by age in these studies, there were no data suggesting that

the drug's efficacy and safety profile differed in paediatric patients versus adult patients apart from tooth discoloration. Overall, these studies support the conclusion that doxycycline is efficacious and well tolerated for the treatment of acne, ASTB, sinusitis, vaginitis, lower respiratory tract infections and acute respiratory tract infections in paediatric patients.

The review of the literature identified numerous articles that focused on paediatric use in the approved indications. No new information regarding efficacy or safety of doxycycline was identified from this review. Overall, doxycycline was found to be efficacious and well tolerated in most the patients treated for different indications such as acne, chlamydial infections, respiratory tract infections, Lyme disease, plague, RMSF, leptospirosis, scrub typhus, malaria, filariasis, pelvic inflammatory disease, trachoma, sinusitis, pneumonia, cholera and treatment of plague.

There were several conditions identified outside the approved doxycycline indications from the literature review. Doxycycline was used intra-lesionally in sclerotherapy for lymphatic malformations, Morel-Lavallee lesions and aneurysmal bone cysts whilst oral doxycycline was used for the treatment of *Mansonella perstans*. Due to the limitations of the study design or the paediatric numbers enrolled, data are considered insufficient to support the addition of these indications to the SmPC. It is noted that no data were provided for the treatment of anthrax, which is a licensed indication in the US.

With regards to the drug safety data provided by the applicant, 17 paediatric cases of tooth discoloration were reported, though it is not known how the cases are stratified by age group or whether the discoloration was considered permanent or temporary. Overall, the MAH's safety database review did not reveal any new safety concerns which may affect the paediatric benefit: risk profile of doxycycline.

Treatment guidelines developed by various organisations recommend doxycycline as the drug of choice in paediatrics for indications such as RMSF, malaria, tick-borne rickettsial disease, Q fever, psittacosis, Lyme disease, malaria and cholera. In a few of the guidelines, doxycycline is not recommended in children aged below 8 years due to the risk of tooth staining; however, this risk depends on the dose and duration of therapy and the disease treated. The rapporteur notes that doxycycline use in children younger than 8 years was documented in a few of the studies from published literature.

The MAH concludes that there is no new efficacy or safety information to support any revisions or additions to the current paediatric-specific text in the Company Core Data Sheet (CDS) and Product Information at this time. With regards to the doxycycline use in children in the EU, there is a contraindication or a warning during tooth development. However, from the MAH-provided data, the rapporteur notes a discrepancy in the age cut off in the doxycycline contraindication for paediatrics between the UK and some EU member states as well as the US.

Doxycycline is a tetracycline derivative and as such its effects and safety is determined to an extent by its class. Most of the doxycycline's reported adverse events from the MAH database and published literature are due gastrointestinal symptoms or skin photosensitivity. However, doxycycline has a lower proportion of adverse effects when compared to other members of its class (Leggat, P.A et al 2009, Smith K et al 2005). Furthermore, as noted in earlier discussions, the incidence of tooth staining is low due to its lower potential to chelate calcium, when compared to other older tetracyclines. Although it might be considered one of the safer members of its class, doxycycline has a contraindication for children younger than 12 years in the UK (or a warning for less than 8 years in some member states) due to its effects on tooth discoloration, enamel hypoplasia and possible bone deposition. This contraindication was historically based on data on the effects of tetracycline, where higher doses and longer courses were used. The submitted studies have presented data that clarify the nature of teeth development in children

and the risk of permanent staining of teeth/ enamel hypoplasia. Apart from the third molars (wisdom teeth), calcification of the permanent teeth enamel is mostly completed by the age of 8 years in children thus the risk of permanent staining in children older than 8 years old is low. Enamel hypoplasia has been reported in infants and children exposed in utero and though evident in those exposed in early childhood, there are other causes of enamel hypoplasia which could occur in this age group. Staining of adult dentition has been known to occur with doxycycline and other tetracycline derivatives by other mechanisms. However, the long-term effects on bone deposition are still not clear. It is therefore concluded that for doxycycline, used in short courses and in the recommended doses, the risk of staining to the permanent dentition in children is low.

It can be argued that the clinical need for treatment of certain infections (such as for malaria or Lyme disease) in children younger than the age of 12 years, is met by the availability of suitable antibiotic alternatives to doxycycline. The low incidence in the UK of other infections (such as Rickettsial disease) may contribute to the infrequent use of this antibiotic. In cases where doxycycline is used in children younger than 12 years, such treatment is usually based on an individual benefit: risk as assessed by the treating clinician, in conditions where no suitable alternatives exist.

It is noted that for cases where doxycycline use in children 8 years and older occurs, there are no observed increases in adverse events. It is therefore possible to consider lowering the age limit for the doxycycline contraindication from 12 to 8 years for licensed indications where no suitable alternatives exist or for cases where the severity of the condition warrants its use.

Leggat, P.A. 2009, "Safety and Efficacy of Doxycycline", Clinical Medicine.Therapeutics, vol. 1.;
Smith K.,et al: Safety of doxycycline and minocycline: a systematic review. Clin Ther 2005; 27: pp. 1329-1342)

- **Conclusion**

The MAH has provided data that support the use of doxycycline for its licensed indications. Data on its use in other paediatric conditions have been provided but are not sufficient to warrant a change of the currently licensed paediatric indications in the SmPC.

No new paediatric safety signals were observed. Although there were reported cases of paediatric tooth staining, no further analysis on type of staining (permanent or primary dentition) or age group involved (including age at use and duration of use) was provided.

The MAH application included use of doxycycline in children younger than 12 years for the licensed indications.

The Rapporteur concludes that based on the data provided as part of this European paediatric work-sharing procedure under Article 45, the positive benefit/risk balance of doxycycline remains unchanged for the paediatric population in the licensed indications. However, it is questioned whether the limitation of its use in children older than 12 years remains appropriate. The MAH is therefore requested to provide additional information, as detailed in the section below.

Request for supplementary information.

1. The MAH is requested to provide details of study DXC-UK-85-001-121 since the PDF file contained another study.

2. The MAH should provide the usage data of doxycycline in children, stratified by age groups <8 years, 8-12 years and 12-18 years.

3. The MAH is requested to provide all available evidence relating to the risk of tooth discolouration in the age group 8 to 12 years, including full details of the 17 cases of tooth staining that were retrieved from the post-marketing database.

Assessment of the response to Questions

1. **The MAH is requested to provide details of study DXC-UK-85-001-121 since the PDF file contained another study.**

MAH Response:

The MAH confirms that information for study DXC-UK-85-001-121 (**Table 6**) was omitted from the initial submission in error and has provided information for this study as part of their response**.**

Table 6 DXC-UK-85-001-121

Study Number Year of the Study Study Design and Objective (s)	**Total Number of Patients (Age Range)**	**Regimen: Formulation, Dose and Duration of the Treatment**	**Baseline data Efficacy Results Safety Results**
DXC-UK-85-001-121 1988 Single-blind, comparative study To compare the efficacy of a low-dose regimen of doxycycline (50 mg once daily) with standard treatment of oxytetracycline (500 mg twice a day) in patients with moderate-to-severe acne vulgaris.	12 (13-38) Paediatric numbers are not available.	Regimen 1: A single once daily dose of doxycycline 50 mg capsule for 12 weeks.	The results showed that most patients in both treatment groups improved, but 2 out of 12 patients in the doxycycline group and 3 out of 16 patients in the oxytetracycline group had more facial lesions at the end of treatment than at the beginning. The patient assessment also showed that a small number of patients failed to improve. The reduction in lesion count was 35% with doxycycline and 34% with oxytetracycline. The overall efficacy was rated as excellent by 2, good by 5, fair by 3 and poor by 2 patients for the doxycycline group, and excellent by 1, good by 8, fair by 5 and poor by 1 patient for the oxytetracycline group. No AEs were seen in any of the treatment groups. **Paediatric numbers are not available. Efficacy data are not stratified by age.**

Rapporteur's comments:

The MAH has provided the study report for DXC-UK-85-001-12; the summary table (Table 6 above) and MAH assessment for this study were included in the original submission. This is the 10th MAH sponsored study to include treatment for acne (which is a licensed indication for doxycycline) and the 6th MAH study to include a comparator. Although paediatric patients were included, age relevant results were not stratified for analysis and as such no separate

assessment of doxycycline's efficacy and safety in children can be made. However, the overall efficacy of doxycycline was similar to oxytetracycline with no reported AEs in either treatment arms. The submitted study has not changed the benefit: risk of doxycycline for the paediatric population.

The MAH concluded that "*there is no new efficacy or safety information to support any revisions or additions to the current paediatric-specific text based on the submitted studies*." With regards to this study the MAH's response is acceptable and the issue is resolved.

2. **The MAH should provide the usage data of doxycycline in children, stratified by age groups <8 years, 8-12 years and 12-18 years.**

MAH Response:

The MAH has enclosed the usage data (**Table 7**) for doxycycline in children, stratified by age groups <8 years, 8-12 years and 12-18 years as requested.

Table 7: Doxycycline usage data in children

Total Number of Written Prescriptions for Doxycycline (Q4 2013 - Q3 2016): RX (Thousands)	Number of Written Prescriptions (Thousands) per quarter												
	Total Number of Written Prescriptions (Thousands)	QTR/12/13 RX	QTR/3/14 RX	QTR/6/14 RX	QTR/9/14 RX	QTR/12/14 RX	QTR/3/15 RX	QTR/6/15 RX	QTR/9/15 RX	QTR/12/15 RX	QTR/3/16 RX	QTR/6/16 RX	QTR/9/16 RX
DOXYCYCLINE	6,320	559	462	451	502	474	498	565	605	610	621	630	342
PFIZER	6,320	559	462	451	502	474	498	565	605	610	621	630	342
Number of Written Prescriptions(Thousands) by Country and Age group													
BRAZIL RETAIL	1,961	132	130	141	172	131	164	144	147	168	209	238	184
All other Patients ages	1,918	128	123	137	171	131	161	141	142	168	206	232	179
Patients 13-18 years	43	5	7	4	2	0	4	3	5	0	3	6	5
ITALY RETAIL	629	60	49	46	44	47	49	52	51	56	53	63	58
All other Patients ages	599	58	47	43	42	45	46	51	49	52	51	59	56
Patients 13-18 years	28	2	2	3	3	2	3	2	1	4	2	3	2
Patients 8-12 years	1	0	0	0	0	0	0	0	0	0	0	0	0
MEXICO RETAIL	386	20	28	18	43	22	29	38	24	32	41	45	46
All other Patients ages	350	17	26	16	37	20	29	36	21	22	41	41	43
Patients 13-18 years	29	3	2	2	6	0	0	0	3	7	0	4	3
Patients 8-12 years	5	0	0	0	0	1	0	0	0	3	0	0	0
Patients <8	2	0	0	0	0	0	0	2	0	0	0	0	0

US DRUGSTORES	650	63	23	27	62	65	48	127	87	74	26	5	43
All other Patients ages	621	63	21	27	57	65	48	115	78	74	24	5	43
Patients 13-18 years	29	0	2	0	5	0	0	12	9	0	2	0	0
ARGENTINA RETAIL	219	39	31	13	12	23	23	7	25	16	10	10	11
All other Patients ages	219	39	31	13	12	23	23	7	25	16	10	10	11
CANADA RETAIL	165	19	15	19	0	18	18	32	13	5	19	8	0
All other Patients ages	154	13	9	19	0	18	18	32	13	5	19	8	0
Patients 13-18 years	11	6	6	0	0	0	0	0	0	0	0	0	0
JAPAN COMBINED	2,307	224	187	187	169	169	165	165	259	259	262	262	0
All other Patients ages	2,037	172	181	181	136	136	151	151	237	237	228	228	0
Patients 13-18 years	245	44	6	6	32	32	14	14	23	23	26	26	0
Patients 8-12 years	25	8	0	0	0	0	0	0	0	0	9	9	0
UK RETAIL	3	1	0	0	0	0	1	0	0	0	1	0	0
All other Patients ages	1	1	0	0	0	0	0	0	0	0	0	0	0
Patients 13-18 years	2	0	0	0	0	0	1	0	0	0	1	0	0

Rapporteur's comments:

The MAH has provided usage data for the Vibramycin (doxycycline) stratified by quarterly number of prescriptions and by age group (less than 8 years, 8 years to 12 years, 13 years to 18 years, and all other patient ages). These data utilise written prescriptions for Vibramycin from 8 countries as surrogate markers for doxycycline use. No further assessment of the data was provided by the MAH.

Based on the rapporteur's assessment of the data, most patients prescribed doxycycline were over the age of 18 years (5,900,000, 93.4% of all prescriptions). The number of doxycycline prescriptions in children under the age of 18 years was 420,000 (6.6% of all prescriptions given within the 3-year period covered).

With regards to the paediatric prescriptions (420,000), 92.1% (387,000, [6.1% of all prescriptions]) were prescribed in children aged 13 years to 18 years, 7.4% (31,000, [0.5% of all prescriptions]) in children 8 years to 12 years and 0.5% (2,000, [0.03% of all prescriptions]) were prescribed in children younger than the age of 8 years. One country (Japan) had the largest proportion of doxycycline paediatric prescriptions (64% or 270,000 prescriptions in children aged 8 years to 18 years) and this likely represents local clinical guidance on the treatment of respiratory infections in children. Japanese Guidelines for the management of respiratory infectious diseases in children (Uehara, S et al 2011, Mikasa, K. et al 2016) state that for children over 6 years old tetracyclines may be given as an alternative to first line antibiotics. They specify use in children younger than 8 years old only when other agents are ineffective or cannot be used. Japanese guidelines for the management of community-acquired pneumonia also state that tetracyclines can be used as 2nd or 3rd line treatment of CAP in conjunction with other antibiotic classes.

The proportion of children who were prescribed doxycycline varied amongst the countries reviewed. Only one country (Mexico) had prescription data in children younger than the age of 8 years whilst another country (Argentina) had no prescription data in patients younger than the age of 18 years. Based on the company's data, the UK had the lowest overall doxycycline prescriptions (<0.05% of all prescriptions, or 3,000 prescriptions) of the 8 countries listed, with most of the prescriptions (66.7% or 2,000 UK prescriptions) in children aged 13 years to 18

years. With regards to the UK prescription data, doxycycline usage is in keeping with the UK contraindication in place for children below the age of 12 years.

Overall these data confirm what has already been described in published literature with regards to doxycycline use in children. Although doxycycline use occurs predominantly in children aged 13 years and older, there is significant use in children younger than the age of 13 years with a very small proportion of prescriptions in children younger than the age of 8 years.

In UK's primary care, doxycycline prescribing data exist for children younger than the age of 12 years and this contrast with the usage data provided by the MAH, where there was no documented doxycycline use in children younger than the age of 13 years. On review of the Clinical Practice Research Datalink (CPRD), between 1st July 2012 to 30th June 2017, approximately 30,607 prescriptions for doxycycline were issued to 14,520 patients aged 18 years or younger. When these prescriptions were stratified per age group there were less than 25 prescriptions in children younger than 8 years, 701 in those aged 8 years to 12 years and 29,893 prescriptions in children aged 13 years to 18 years. This difference between the CPRD data and those of the MAH could be due to the use of other generic doxycycline products in UK primary care. Although the quality of data held in the CPRD database is subject to rigorous checks it contains data on prescriptions rather than actual usage hence non-compliance with the treatment instructions cannot be studied or commented upon. CPRD captures prescriptions issued in primary care, but does not capture prescriptions issued in secondary care.

There are also several limitations with the assessment of MAH's Vibramycin prescription data. Written doxycycline prescriptions provide only a surrogate marker for actual doxycycline use and as this data provided for Vibramycin, it cannot capture all doxycycline use in children across all MSs and the various products available. In addition, these data do not provide information on patient adherence to doxycycline treatment, what formulations were used or how many repeat prescriptions were given. It also remains unknown the indications for treatment with doxycycline and the duration of such treatment. Furthermore, it cannot be ascertained from the data provided what proportion of doxycycline was prescribed in accordance with the country specific labelling for doxycycline, if it was prescribed off label to address an individual patient's clinical need or what whether there were safety issues reported. This is of interest in 3 countries listed (Italy, Mexico and Japan) where prescriptions for children aged 12 years and younger were recorded.

Conclusion:
The usage data for Vibramycin confirm that there is significant use of doxycycline in children under the age of 12 years with a very small proportion of usage occurring in children under the age of 8 years.

Uehara, S et al (2011), Japanese Guidelines for the Management of Respiratory Infectious Diseases in Children 2007 with focus on pneumonia. Pediatrics International, 53: 264–276. doi:10.1111/j.1442-200X.2010.03316.x.

Mikasa, Keiichi, et al. "JAID/JSC Guidelines for the Treatment of Respiratory Infectious Diseases: The Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy - the JAID/JSC Guide to Clinical Management of Infectious Disease/Guideline-Preparing Committee Respiratory Infectious Disease WG." Journal of Infection and Chemotherapy : Official Journal of the Japan Society of Chemotherapy, vol. 22, no. 7 Suppl, 2016, pp. S1-S65.

3. **The MAH is requested to provide all available evidence relating to the risk of tooth discolouration in the age group 8 to 12 years, including full details of the 17 cases of tooth staining that were retrieved from the post-marketing database.**

MAH Response:

Tooth discoloration is known to be associated with the tetracycline class. However, the potential risk of clinically significant tooth discoloration is lower with doxycycline than with other tetracyclines, probably because doxycycline binds to calcium less than other tetracyclines, (19.0% for doxycycline vs 36.0% for oxytetracycline, 39.5% for tetracycline, 39.5% for methacycline, and 74.5% for demethylchlortetracycline). Several clinical studies indicated that treatment with doxycycline in children is not associated with permanent tooth discoloration. However, no study specifically among children aged 8-12 years has been identified. Only one small sample size study by Lochary et al included children who were equal or older than 8 years old. Lochary et al examined 10 children who received doxycycline for Rocky Mountain Spotted Fever (RMSF). The mean age of the study subjects was 13.7 years (range, 11 to 19 years), and the average age at exposure was 5.1 years. The age at exposure of doxycycline ranged from 4 1/3-year-old to 8 ¼ -year-old, including one child aged 8 years old and the other aged 8 ¼ years old. Each study subject was matched with two control subjects. There was no statistically significant difference (P = 0.38) between study and control subjects in the incidence or degree of staining of the teeth. Forti reported that 25 premature infants who received doxycycline for 6 to 17 days were examined 1 year later. Only one child had a slight spotted discoloration of the upper incisors. The studies by Volovitz et al and Todd et al included children who had been treated with doxycycline before the age of 8 years. No tooth staining was detected in either study.

Reversible, extrinsic discoloration of adult teeth has been reported with doxycycline in the literature. In these published case reports, 6 patients, aged from 12 to 28 years old, received a 30-45-day course of doxycycline therapy at a dose of 200mg/day. Out of the 5 patients, 2 patients were aged 12 years old. However, the discoloration of adult teeth in these patients was likely due to extrinsic rather than intrinsic staining since the discoloration was removable with professional dental cleaning.

The literature evidence relating to the risk of tooth discoloration in the age group 8 to 12 years is minimal. However, the available published literature does not indicate the correlation between the use of doxycycline and tooth discoloration in children less than 8 years.

Safety database: The ages of the 17 cases of tooth discoloration are shown in **Table 8** below.
The MAH has updated sections 4.4 and 4.8 of the Company Cored Data Sheet(s) (cCDSs) to add text regarding Tooth discoloration (effective date: 06-OCT-2016). Variation applications are being submitted to update the Product Information in line with the CDSs. The Clinical Overview to support this update is enclosed.

Table 8: Cases of tooth discoloration	
Case	Age in years
Case 1	0.58
Case 2	0.63
Case 3	2
Case 4	2
Case 5	5
Case 6	8
Case 7	8
Case 8	12
Case 9	12
Case 10	13
Case 11	14
Case 12	14
Case 13	14
Case 14	16
Case 15	16
Case 16	16
Case 17	17

Rapporteur's comments:

The MAH has provided reports on teeth staining from their database as well as from published literature. With regards to the MAH safety database, there were 17 cases of tooth staining attributed to doxycycline use in children younger than the age of 18 years. Eight (8) patients were older than 12 years, two were aged 12 years and there were 7 children who were younger in age, ranging from 7 months to 8 years. Two (2) of the 7 cases were exposed in utero. Due to limited information, it could not be reliably determined if the reported cases in children younger than 8 years had permanent discoloration of dentition. The MAH concluded that for children older than the age of 8 years, doxycycline caused reversible discolouration of permanent teeth, however this cannot be substantiated by the limited data available. Of note, there were also two cases of enamel hypoplasia reported in the MAH safety database, one in a 25-year-old and the age of the other case was not known.

The exact incidence of the tooth staining in children after doxycycline use is not known. However, the MAH calculated a point estimate for this ADR based on published clinical trials and case reports, where the numbers of patients who received doxycycline and the type of adverse events were known. Based on their calculations, they considered the ADR to be rare, occurring at a rate of 1/1277 or lower.

With regards to published literature on tooth staining from doxycycline, two comparative studies and two observational studies were assessed by the MAH. These 4 studies (*Forti et al, Lochary et al as well as Volovitz et al and Todd et al discussed previously*) were conducted in children who were prescribed doxycycline before the age of 8 years. Lochary et al 1998, was a retrospective study of children who received doxycycline for the treatment of Rocky mountain spotted fever (RMSF) between May 1981 to August 1988, with each study subject matched with two controls. Photographs of the teeth were compiled and coded with the study teeth identified by an arrow. Photographs of complementary teeth in the matched controls were similarly mounted and identified. Residents in dentistry served as the independent assessors, who were blinded to study groups. Initially 36 children were identified with the diagnosis of RMSF, however 10 children participated in the study. The mean age of the study subjects was 13.7 years

(range, 11 to 19 years), and the average age at exposure was 5.1 years. There was no statistically significant difference (*P* = 0.38) between study and control subjects in the incidence or degree of staining of the teeth.

From the analysis of the published studies, there was no significant evidence of permanent tooth staining from doxycycline use in children when compared to either matched controls or after a significant period of follow up. Although these data are limited by small paediatric numbers and the retrospective nature of data collection, they provide evidence in support of the low risk of long term effects to dentition from doxycycline use in early childhood.

A review of Yellow Card reports made to the MHRA (from 1965) up to 30th June 2017, noted that there has been a total of 10 reports for tooth discoloration or tooth disorders related to doxycycline use in all age groups. It is not known if these cases of tooth staining were classed as permanent or temporary. Three (3) cases were reported in adults and there was 1 case report where the age was unknown. There were 6 paediatric cases between the ages of 0 to19 years-one in the 0 to 9-year age range and 5 reported in patients aged between 10 years to 19 years. Four (4) of the paediatric cases were non-serious, 2 were classed as serious. These data contrast with the safety data provided by the MAH and suggest that there may be under reporting of this ADR.

Based on the available data, tooth staining from doxycycline is a risk at any age, but there are different mechanisms involved in tooth staining in young children when compared to children over 10 years of age. The greatest risk for irreversible, tooth discolouration occurs during two critical periods of tooth development: the first is during calcification of deciduous teeth which occurs from approximately the end of the fourth month of gestation to 11 to 14 months postnatally. The second risk period occurs during calcification of permanent dentition which usually commences at the age of 30 to 36 months and is completed for most teeth (apart from the third molars) by the age of 7 to 8 years (Sánchez, A. et al 2004). For third molars (wisdom teeth), calcification occurs later, from the age of 7 years to 10 years and as such there is a risk (although lower) of permanent staining of these teeth if doxycycline exposure occurs in children after the age of 8 years. From the data provided by the MAH safety database, published literature and yellow card reports, tooth staining from doxycycline appears to be a rare event and could be reduced using shorter doxycycline courses or alternative treatments, if available, in young patients. Although tooth staining is known tetracycline class effect, the frequency and severity is significantly lower for doxycycline compared to other agents in its class due to its lower potential for chelating calcium which makes it less likely to permanently discolour teeth.

Doxycycline is an old drug; its safety profile is well established and no new safety signals have been noted through the data submitted in this work-sharing procedure. It is acknowledged that the available data on tooth staining are limited given the overall low (albeit significant) use in children but provide reassurance with regards to this safety risk in children. These data clarify that in children, if doxycycline is used for short courses and where no suitable alternatives exist, the benefit of doxycycline treatment might outweigh the (rare) risk of tooth staining.

The available data are insufficient to warrant the addition of any new indications in children for doxycycline.

However, these data are deemed sufficient to reduce the restriction age-cut off based on the safety risk of tooth staining in children from 12 years to 8 years. For children above the age of 8 years, the risk of irreversible discolouration of permanent teeth due to doxycycline is limited to the third molars (wisdom teeth). Short courses of doxycycline and limiting its use to acute infections were few alternative treatments exist, help further mitigate this risk. The assessed

data provide reassurance of the low risk of permanent tooth discoloration in children aged 8 years to less than 12 years and demonstrate that there are no new reported safety signals to justify the contraindication for doxycycline use in this age group. Therefore, doxycycline's restriction of paediatric use due to the risk of teeth staining in children aged 8 years to less than 12 years is not supported.

The rapporteur also considers it appropriate to replace the contraindication for children younger than 8 years old with a warning based on the risk of tooth staining in the SmPC.

From the presented data, there is evidence of low (off label) use of doxycycline in children younger than the age of 8 years. There are few life-threatening conditions, (such as RSMF) where no suitable antibiotic treatment alternatives exist and where the risk: benefit of doxycycline might be favourable to justify treatment in young children. There are also infections due to drug resistant organisms (such as macrolide resistant mycoplasma infections), which limited effective antibiotic options are available and in such cases, the benefits of doxycycline treatment in individual patients might outweigh the risk of tooth staining. Although there is low (off label) use of doxycycline and possible under-reporting of tooth staining in children aged younger than 8 years, the low incidence of tooth staining may represent doxycycline's lower affinity for chelation compared with other tetracycline agents.

Overall there remains a small yet significant cohort of patients younger than the age of 8 years, with severe infections where no suitable or effective treatment options exist, in whom doxycycline treatment might be considered favourable based on an individual benefit: risk as assessed by the treating clinician. Since there remains a risk of irreversible staining of permanent dentition during their period of calcification, there is sufficient rationale to recommend a warning for doxycycline use in children younger than 8 years of age.

Sánchez, A. et al. (2004), *Tetracycline and other tetracycline-derivative staining of the teeth and oral cavity. International Journal of Dermatology*, 43: 709–715. doi:10.1111/j.1365-4632.2004.02108.x

Additional MAH Response:

On 21st October 2015, the Marketing Authorization Holder (MAH) received a communication from the United States (US) Centers for Disease Control (CDC) regarding a recent published study (Todd et al 2015 discussed earlier in this procedure), which showed that there was no visible dental staining in children treated with doxycycline for suspected Rocky Mountain Spotted Fever (RMSF). The CDC noted that the current Warnings and Precautions sections of the United States package inserts (USPI) may not accurately reflect the risks of permanent tooth discolouration in paediatric populations with doxycycline use, and the language may deter clinicians from providing doxycycline for treatment of paediatric cases of RMSF. On 04 November 2015, the MAH received email communication from the FDA including proposed revisions to the labels. The FDA requested to revise Warnings, Precautions, Paediatric Use, and Dosage and Administration sections of the USPI.

The revision was aimed to emphasize the use of doxycycline in paediatric patients only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g. anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies, because of the effects of drugs of the tetracycline-class, including doxycycline, on tooth development and growth. Permanent discolouration of the teeth and enamel hypoplasia are included as a class warning on the use in children in the Special warnings and precautions for use section of the current doxycycline core data sheets (CDSs) (effective 18 December 2015). The update to this section was triggered by evaluations conducted following the FDA

request. In addition, the aim of this review is to evaluate the available data in the MAH safety database and in the literature, to determine whether there is sufficient evidence to categorize tooth discolouration or enamel hypoplasia as ADRs of doxycycline.

Based on the available data, the MAH has updated safety information of doxycycline CDSs with the revision of warning for tooth discolouration in children in section **4.4, Special warnings and precautions for use** and the addition of the ADR Tooth discolouration to section **4.8, Undesirable effects**. The revision is planned because the doxycycline CDSs do not reflect the current knowledge on the risks and benefits of doxycycline therapy in children up to and including the age of 8 years. For example, administering short courses of doxycycline for 10 days or less to children younger than 8 years of age for treatment of RMSF has not been shown to cause visible tooth staining in children nor have there been any cases of permanent tooth discolouration regardless of age in the safety database. Further, doxycycline is the first-line therapy for the treatment of suspected RMSF in children, recommended by both CDC and the American Academy of Pediatrics (AAP) Committee on Infectious Diseases. Use of antibiotics other than doxycycline increases the risk of patient death.

The MAH states that the updates made to the doxycycline CDSs are intended to provide the most up-to-date information on the safe and effective use of doxycycline. The overall benefit-risk profile of doxycycline remains favourable for the approved indications, when used in accordance with the product information. The MAH will continue to monitor reports of AEs associated with doxycycline and will revise the product documents, if deemed necessary.

Rapporteur's comments:

The Rapporteur notes that the MAH was recently requested by the FDA to revise the US label for Vibramycin, with the aim to clarify doxycycline use in the treatment of certain infections in children younger than the age of 8 years and to emphasize that doxycycline can be used in paediatric patients in this age group only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (such as Rocky Mountain spotted fever).

In the provided clinical overview document, the MAH proposes changes to Section 4.4 and 4.8 of the Core Data Sheet (CDS) for doxycycline, clarifying the warning for doxycycline use in children younger than the age of 8 years. However, the applicant proposes no updates to posology for doxycycline in children aged 8 years to less than 12 years as these are already contained in the CDS.

Overall Discussion

Efficacy:
Doxycycline efficacy for its licensed indications in children aged 8 years and older is confirmed by the assessed data. Although doxycycline was used off label for the treatment other paediatric conditions, there was no robust evidence to support doxycycline efficacy in these unlicensed indications.

Safety:
No new safety signals have emerged for doxycycline in any of the assessed studies. The most commonly reported ADRs in children in all age groups are already described in the SmPC and comparable with those reported in clinical practice. Tooth staining is a known adverse event associated with tetracyclines, but this adverse event is rarely reported for doxycycline. This may

be due to the doxycycline's lower risk for tooth staining and to possible under reporting of this ADR, along with the low use in young children. Although the causes of under-reporting may not be known, one factor could be the individual clinician's perception that this adverse event may be acceptable when patients require doxycycline treatment for severe infections.

Contraindication in children aged 8 years to 12 years old:
In this age group, the risk of irreversible discolouration of permanent teeth due to doxycycline is limited to the period of calcification of the third molars (wisdom teeth) which occurs between the ages of 7 years to 10 years. Short courses of doxycycline and limiting its use to acute infections were limited alternative treatments exist, help further mitigate this risk. The assessed data provide reassurance of the low risk of permanent tooth discoloration in children aged 8 years to less than 12 years and demonstrate that there are no other reported safety signals which support the restriction for doxycycline use in this age group.

Contraindication in children younger than 8 years old:
As noted with older children, the low incidence of teeth staining reported in this age group may represent doxycycline's lower affinity to cause tooth staining compared with other tetracycline agents although it is acknowledged that this effect may be confounded by the low use of doxycycline and possible under-reporting of this ADR in this age cohort. In addition, there are no new safety signals that have emerged for doxycycline in children younger than 8 years old.

There remain potentially serious and life threatening infections (such as RSMF, other rickettsial infections) in young children where no suitable antibiotic treatment alternatives exist. In these cases, the risk: benefit of doxycycline might be favourable to justify its use. There are also infections (such as in macrolide resistant mycoplasma infections) where increasing levels of antimicrobial resistance limit the availability of effective antibiotic options thus the benefits of doxycycline treatment in these individual patients might outweigh the risk of tooth staining.

In summary, these data support the removal of the contraindication based on tooth staining in children younger than 12 years. They also support the inclusion of a warning in Section 4.4 of the SmpC and CDS for doxycycline use in children aged younger than 8 years as there remains a potential risk of irreversible staining to permanent dentition in this age group to allow its use where no alternatives exist.

Posology:
There are dosing data available in the MAH's CDS for doxycycline for children 8 years and older. Doxycycline posology is also available in certain EU SmPCs (Sweden) for this age group. Several US based guidelines (such those for the treatment of RMSF, anthrax and malaria from the Centers for Disease Control, The American Academy of Pediatrics, and the WHO Global Task Force guidelines on cholera) as well as the US label for doxycycline also include dosing recommendations for children 8 years and older. Several of the studies on infections in the literature review assessed doxycycline treatment in children younger than 12 years compared to other established antibiotic treatments and were considered robust to support dosing in the children aged 8 years to 12 years.

Proposed SmPC changes:
Although the MAH has not proposed changes to paediatric posology or to doxycycline indications in the CDS, there are inconsistencies (as noted earlier in this assessment) in the doxycycline CDS, certain SmpCs across EU member states and the UK SmpC. In Section 4.3 of the UK SmPC, a contraindication exists for doxycycline below the age of 12 years however, other EU SmPCs have this is as either a contraindication or as a warning (such as the Swedish Vibramycin SmPC) only in children up to the age of 8 years. Posology is thus available in some EU member states for children from the age of 8 years.

There is a need to provide clarity in the information contained within all EU SmPCs, to reduce off label use of doxycycline, to promote safe, judicious prescribing in keeping with good antimicrobial stewardship practices and to simplify the variable warnings and contraindications (derived from the same data assessed in this procedure) that exist for this product within EU member states. Therefore, based on previous discussions, Sections 4.1, 4.2, 4.3, 4.4 and 4.8 of the UK SmPC should also be updated as noted in Section V below.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall Conclusion**

The MAH has provided data that support the use of doxycycline for its licensed paediatric indications. Although data on doxycycline's off label use in other paediatric conditions have been provided, it is not sufficiently robust to warrant inclusion of any new paediatric indications in the SmPC.

No new paediatric safety signals were observed. Doxycycline is an established drug, with a few reported cases from the MAH safety data base and from published literature on paediatric tooth staining. There is a paucity of information on whether these cases resulted in permanent discoloration.

There is reported use of doxycycline in children younger than 12 years with a small proportion of patients being children younger than the age of 8 years. However, in younger children these data are limited regarding the information on the indications treated, dosing and to the duration of therapy. Data from published literature confirm that doxycycline use in children younger than 12 years in approved and off label indications was not associated with any new safety signals.

There are inconsistencies in the EU SmPCs for doxycycline with regards to use in children. Contraindications exist for children either from the age of 8 years or 12 years due to the risk of tooth staining. In some EU member states, only a warning exists for such use in children.

The assessed doxycycline data from this Article 45 work sharing procedure change the overall benefit: risk profile of doxycycline in children, and provide reassurance on the safety of doxycycline regarding the low potential risk of tooth staining in children. These data demonstrate that doxycycline can be used safely in children aged younger than 12 years in the treatment of severe or life-threatening conditions, when the potential benefits are expected to outweigh the risks, and where no suitable alternatives exist. Therefore, the assessed data are sufficient to support the lifting of the contraindication as listed in section 4.3 of the UK Vibramycin SmpC, in children younger than the age of 12 years and the replacement with a warning in children younger than the age of 8 years.

Member States' comments:
Member states' comments were received on the proposed change to the contraindication in children and to the proposed SmPC/PIL wording. These comments have been addressed in the final recommendation of this report. Overall, there was agreement with the Rapporteur's conclusions and final recommendations. The procedure is therefore considered finalised.

- **Recommendation**

The assessed data are sufficient to support the lifting of the contraindication as listed in section 4.3 of the UK Vibramycin SmpC, in children younger than the age of 12 years and the replacement with a warning in children younger than the age of 8 years. Furthermore, these data are insufficient to recommend any new indications for doxycycline use.

Modifications are proposed in Sections 4.1, 4.2, 4.3, 4.4 and 4.8 of the Vibramycin SmpC and the PIL that are applicable to all similar products with a license for use in children. For member states with unrestricted doxycycline use in children aged 8 years to 12 years, the proposed precautionary statement for this age group will not be a mandatory requirement of this Article 45 work-sharing procedure. Furthermore, the exact text of the precautionary wording should be adapted to the approved indications of the respective products in individual member states.

These changes should be submitted to national competent authorities for review via a variation procedure. A variation is hereby requested from the MAH within 90 days of publication of the PAR. The newly proposed SmpC and PIL texts are *italicized* and underlined and the deleted text is ~~strike through~~.

- **Proposed changes to the SmPC.**

4.1 Therapeutic indications

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults *and children aged 12 years to less than 18 years*

The usual dosage of Vibramycin for the treatment of acute infections in adults *and children aged 12 years to less than 18 years* is 200 mg on the first day (as a single dose or in divided doses) followed by a maintenance dose of 100 mg/day. In the management of more severe infections, 200 mg daily should be given throughout treatment.

Children aged 8 years to less than 12 years. (Section 4.4)

The use of doxycycline for the treatment of acute infections in children aged 8 years to less than 12 years should be carefully justified in situations where other drugs are not available, are not likely to be effective or are contraindicated.
In such circumstance, the doses for the treatment of acute infections are:
For children 45 kg or less- Initial dose: 4.4 mg/kg (in single or 2 divided doses) with maintenance dose: 2.2 mg/kg (in single or 2 divided doses). In the management of more severe infections, up to 4.4 mg/kg should be given throughout treatment.
For children, over 45 kg - Dose administered for adults should be used.

Children aged from birth to less than 8 years.

Doxycycline should not be used in children aged younger than 8 years due to the risk of teeth discolouration. (Section 4.4 and 4.8)

4.3 Contraindications

Hypersensitivity to doxycycline or to any of the tetracyclines or to any of the excipients listed in section 6.1.
~~The use of drugs of the tetracycline class during tooth development (pregnancy, infancy and childhood to the age of 12 years) may cause permanent discolouration of the teeth (yellow-grey-~~

~~brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Vibramycin is therefore contraindicated in these groups of patients~~.

Pregnancy Vibramycin is contraindicated in pregnancy. It appears that the risks associated with the use of tetracyclines during pregnancy are predominantly due to effects on teeth and skeletal development. (See *Section 4.4* ~~above about~~ *regarding* use during tooth development).

Nursing mothers Tetracyclines are excreted into milk and are therefore contraindicated in nursing mothers. (See *Section 4.4* ~~above about~~ *regarding* use during tooth development).

~~Children: Vibramycin is contraindicated in children under the age of 12 years. As with other tetracyclines, Vibramycin forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracyclines in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. (See above about use during tooth development).~~

4.4 Special warnings and precautions for use

Paediatric population

The use of drugs of the tetracycline class during tooth development (last half of pregnancy; infancy and childhood to the age of 8 years) may cause permanent discolouration of the teeth (yellow-grey-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Use doxycycline in paediatric patients aged younger than 8 years only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g. ~~anthrax,~~ Rocky Mountain spotted fever), ~~particularly~~ only when there are no adequate alternative therapies.

Although the risk of permanent teeth staining is rare in children aged 8 years to less than 12 years, the use of doxycycline should be carefully justified in situations where other drugs are not available, are not likely to be effective or are contraindicated.

~~Doxycycline, therefore, should not be used in these groups of patients unless other drugs are not available, are not likely to be effective or are contraindicated. However, doxycycline may be used for anthrax, including inhalational anthrax (post-exposure) in these groups of patients.~~

4.8 Undesirable effects

Adverse Drug Reaction Table

System Organ Class	Adverse Drug Reaction
Gastrointestinal disorders	Pancreatitis, Pseudomembranous colitis, Clostridium *difficile* colitis, Oesophageal ulcer, Oesophagitis, Enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, Dysphagia, Abdominal pain, Diarrhoea, Nausea/Vomiting, Dyspepsia (heartburn/gastritis), Glossitis, *Tooth discolouration* [a]
Reversible and superficial discolouration of permanent teeth has been reported with the use of doxycycline but frequency cannot be estimated from available data	

Adverse Drug Reaction Category Overview Table

System Organ Class	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000	*Frequency Not known*
Gastrointestinal disorders	Nausea/vomiting	Dyspepsia (Heartburn/gastritis)	Pancreatitis, Pseudomembranous colitis, Clostridium difficile colitis, Oesophageal ulcer, Oesophagitis, Enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, Dysphagia, Abdominal pain, Diarrhoea, Glossitis, ~~*Tooth discolouration*~~ *a*	*Tooth discolouration* *a*
a. Reversible and superficial discolouration of permanent teeth has been reported with the use of doxycycline but frequency cannot be estimated from available data				

- **Proposed changes to the Package leaflet**

Newly added text is *italicized* and underlined and the deleted text is ~~strike through~~.

2. What you need to know before you take Vibramycin-D

Do not take Vibramycin-D:

- if you are allergic to doxycycline or any other tetracycline antibiotic or any of the other ingredients of this medicine (listed in section 6)
- if you are pregnant or trying to become pregnant
- if you are breast feeding
- ~~if the medicine has been prescribed for a child under the age of 12 years~~

You should not use Vibramycin-D during periods of tooth development (pregnancy, infancy or in children below ~~12~~ *8* years old) as such use may lead to permanent discolouration (yellow-grey-brown) or affect the proper growth of the teeth.

There may be circumstances (e.g., severe or life-threatening conditions), where your physician may decide that the benefits outweigh this risk in children below 8 years and Vibramycin should be prescribed.

3. How to take Vibramycin-D

Always take this medicine exactly as your doctor or pharmacist has told you to. Check with your doctor or pharmacist if you are not sure.

The recommended doses are shown in the list below. These are the different doses that your doctor may prescribe depending on the infection being treated.

Usual Dose (Chest, lung or nasal, urinary tract, eye and other infections)

Children aged 8 years to less than 12 years:

Doxycycline for the treatment of acute infections in children aged 8 years to less than 12 years should be used in situations where other drugs are not available or are not likely to be effective. In such circumstances, the usual doses are:

For children 45 kg or less:
First day: 4.4 mg for each kg of bodyweight (in single or 2 divided doses) then 2.2 mg for each kg of bodyweight (in single or 2 divided doses) from the second day. The length of treatment is dependent on the infection being treated.
In more severe infections, up to 4.4 mg for each kg of bodyweight should be given throughout treatment.

For children, over 45 kg - Dose administered for adults should be used; 200mg on the first day, then 100 mg daily. The length of treatment is dependent on the infection being treated.

Adults and children aged 12 years to less than 18 years:
200mg on the first day, then 100 mg daily. The length of treatment is dependent on the infection being treated.

4. Possible side effects

Rare: may affect up to 1/1000people

- difficulty in swallowing, sore or painful tongue or mouth
- skin reddening (flushing)
- a ringing or buzzing noise in the ear
- soreness and itching of the rectal and/or genital area
- inflammation of the bowel
- bulging fontanelles (soft spot on head) of infants
- increased pressure in the skull (severe headache with change in vision)
- inflammation and damage to the liver
- abnormal liver function tests
- discolouration of the thyroid tissue when given for long periods. The medicine does not impair thyroid function
- loosening of the nail from the nail bed after exposure to the sun
- increased levels of urea in the blood
- yellow skin and eyes (jaundice), inflammation of the pancreas
- upset stomach, loss of appetite, diarrhoea (this may occur up to two or three months after the last dose), stomach pain
- ~~*discolouration and/or lack of growth of teeth*~~

Not known: frequency cannot be estimated from the available data

- *discolouration and/or lack of growth of teeth*

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	Name of medicinal product	Pharmaceutical form	Strength	Active Ingredient
Pfizer	Vibramycin	Capsules	50, 100 or 200 mg	Doxycycline Hyclate
		Film-coated tablets	50 or 100 mg	Doxycycline Hyclate
		Dispersible tablets	100 mg	Doxycycline Monohydrate
		Syrup	10 mg/mL	Doxycycline Hyclate (also referred to as Doxycyline Calcium Syrup)
			10 mg/mL	Doxycycline Monohydrate
		Solution for Injection	100 mg/5 mL	Doxycycline Hyclate