

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Moderate to severe acne

Acne vulgaris is a common inflammatory pilosebaceous disease; it is so common that it is often referred to as a physiological condition. Research has shown that 85% of young people between the ages of 12 and 24 years have acne, and while it is most common in teenagers, acne affects 8% of adults aged 25 to 34 years and 3% of adults aged 35 to 44 years. Acne in young adults may represent continuation of adolescent acne or development of late-onset disease. Acne is more common in boys than girls during adolescence, but the incidence is higher in women during adulthood. Nodulocystic acne has an increased prevalence in white people compared to black people. Prevalence varies greatly across the world, with Western modernised civilisations demonstrating much higher rates of acne, whereas some non-industrialised societies report no cases of acne. Acne vulgaris affects 40 to 50 million people annually in the US.

Acute sinusitis

Acute sinusitis (also commonly known as acute rhinosinusitis) is a symptomatic inflammation of the mucosal lining of the nasal cavity and paranasal sinuses, where clinical symptoms have been present for 4 weeks or less. It can be caused by either a viral or a bacterial infection.

More than 20 million cases of acute sinusitis of viral or bacterial aetiology are diagnosed in the US each year across all age groups, affecting an estimated 16% of the adult population and resulting in almost 12 million surgery visits per year. Approximately 0.5% to 13% of viral upper respiratory tract infections progress to acute bacterial sinusitis. It is estimated that 6% to 13% of children will have had one case of acute sinusitis by the age of 3 years.

Although the bacterial pathogens have not changed over time, their antibiotic-resistance patterns have altered.

Acute exacerbation of chronic bronchitis

Bronchitis is an inflammation of the bronchial tubes, the airways that carry air to your lungs. It causes a cough that often brings up mucus, as well as shortness of breath, wheezing, and chest tightness. There are two main types of bronchitis: acute and chronic.

Chronic bronchitis is one type of COPD (chronic obstructive pulmonary disease). The inflamed bronchi produce a lot of mucus. This leads to cough and difficulty getting air in and out of the lungs. Cigarette smoking is the most common cause. Breathing in other fumes and dusts over a long period of time may also cause chronic bronchitis. Treatment will help symptoms, but chronic bronchitis is a long-term condition that keeps coming back or never goes away completely¹.

Acute exacerbations of chronic bronchitis and COPD are the main causes of medical visits and hospitalizations, resulting in economic costs in excess of \$5 billion yearly. In one prospective series, the costs of treating COPD and ABECB were found to be almost twice those reported for asthma. The

¹ Present in <http://www.nlm.nih.gov/medlineplus/chronicbronchitis.html> on 08/04/2015



prevalence of COPD, and thus the prevalence of ABECB, continues to rise as the population ages, and it is the only leading cause of death for which the mortality rate is currently increasing².

Helicobacter pylori infection

Helicobacter pylori is a gram-negative flagellated spiral bacterium found in the stomach. Infection with H. pylori is predominantly acquired in childhood. H. pylori infection is not associated with a specific type of dyspeptic symptom. The organism is associated with lifelong chronic gastritis and may cause other gastroduodenal disorders.

In the developed world, H. pylori prevalence rates vary with year of birth and social class. Prevalence in many resource-rich countries tends to be much higher (50% - 80%) in individuals born before 1950 compared with prevalence (< 20%) in individuals born more recently. In many resource-poor countries, the infection has a high prevalence (80% - 95%) irrespective of the period of birth. Adult prevalence is believed to represent the persistence of a historically higher rate of infection acquired in childhood, rather than increasing acquisition of infection during life.

Overcrowded conditions associated with childhood poverty lead to increased transmission and higher prevalence rates. Adult reinfection rates are low: less than 1% a year³.

Urogenital infections caused by Chlamydia trachomatis

Urogenital chlamydia infection is a common sexually transmitted diseases (STD) worldwide. The causative organism is Chlamydia trachomatis. Infection is usually asymptomatic in both men and women. In women, the infection tends to occur in the endocervical canal and some women who have uncomplicated cervical infection already have subclinical upper reproductive tract infections upon diagnosis. Symptoms may include intramenstrual or postcoital bleeding; an odourless, mucoid vaginal discharge; pelvic pain; or dysuria. In men, infection can occur in the urethra, causing a penile discharge. Untreated or inadequately treated infections can lead to more serious problems such as pelvic inflammatory disease (PID), ectopic pregnancy, and infertility in women, and epididymitis and prostatitis in men.

Infections are caused by the bacterium Chlamydia trachomatis, which is almost always transmitted by sexual contact, and it is one of the most commonly reported sexually transmitted infections. The bacterium may cause symptoms, but in most people the infection is asymptomatic⁴.

Trachoma

Trachoma is a keratoconjunctivitis caused by ocular infection with Chlamydia trachomatis (serovars A, B, Ba, and C). It should not be mistaken for chlamydial conjunctivitis, which is a self-limiting conjunctivitis caused by the sexually transmitted strains of Chlamydia (serotypes D to K). Inflammatory episodes in adults tend to be shorter and less severe than in children. Repeated infections lead to recurrent episodes of chronic inflammation that may progress to scarring of the upper tarsal conjunctiva. The scarring results in distortion of the upper eyelid, and this can cause lashes to abrade the cornea. This is called trachomatous trichiasis and, unless surgically corrected, will rapidly lead to corneal opacity and blindness.

Worldwide, trachoma remains endemic in 54 countries. It is confined to regions of disadvantage in Africa, the Middle East, Asia, Latin America, the Pacific Islands, and remote Aboriginal communities in Australia.

² Present in <http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/pulmonary/acute-bacterial-exacerbation-chronic-bronchitis/> on 08/04/2015

³ Present in <http://bestpractice.bmj.com/best-practice/evidence/background/0406.html> on 08/04/2015

⁴ Present in <http://bestpractice.bmj.com/best-practice/monograph/52.html> on 08/04/2015

Approximately 84 million people have active trachoma, another 7.6 million have trichiasis, and 1.3 million of these people are blind⁵.

Trachoma is the leading cause of infectious blindness worldwide⁶.

Rickettsiosis

Rocky Mountain spotted fever (RMSF) is a systemic vasculitis caused by infection with *Rickettsia rickettsii*, a tick-borne, gram-negative, intracellular bacterium. It is the most common rickettsial infection in North America and the most commonly fatal tick-borne infection in the US. Fever, rash, headache, and vomiting are the most common manifestations, but virtually any organ may be affected.

RMSF only occurs in the western hemisphere. From 1993 to 2002, the average annual incidence of RMSF in the US was 2.2 cases per million people, and the incidence was highest in the south central and south Atlantic regions. Cases have also been confirmed in Canada, Mexico, and Central and South America. From 1981 to 1996, the incidence was highest in children aged 5 to 9 years; however, from 1997 to 2002, the peak incidence was in adults aged 60 to 69 years. Sixty percent of cases occur in males. White people account for 88% of cases, and black people and members of other ethnic groups account for 7% and 5% of cases, respectively. Because RMSF is transmitted by ticks, it is often diagnosed in people who reside (or have recently spent time) in wooded or rural settings. Many cases, however, have been reported from urban areas such as New York City. RMSF is most common in the spring and summer; 90% of cases occur between 1 April and 30 September. However, cases do occur in winter months, even in areas with cold winters⁷.

Soft tissue infection

Skin and soft tissue infections (SSTIs) are clinical entities of variable presentation, etiology and severity that involve microbial invasion of the layers of the skin and underlying soft tissues. SSTIs range from mild infections, such as pyoderma, to serious life-threatening infections, such as necrotizing fasciitis. The minimum diagnostic criteria are erythema, edema, warmth, and pain or tenderness. The affected area may also become dysfunctional (eg, hands and legs) depending on the severity of the infection. A patient's comorbidities (eg, diabetes mellitus and HIV) can easily transform a normally mild infection into a rapidly advancing threat to life. SSTIs present clinically diverse challenges requiring management strategies that efficiently and effectively identify those cases requiring immediate attention and intervention, whether medical or surgical, from those less severe cases.

Overall, the rate of complicated cellulitis is low (erysipelas 0.09 per 1000 person-years; lymphadenitis 0.16% of all cellulitis cases; lymphangitis 0.16 per 1000 person-years and necrotizing fasciitis 0.04 per 1000 person-years)[1].

VI.2.2 Summary of treatment benefits

Given that lymecycline is metabolized to its parent compound, tetracycline, before being absorbed, many of its properties fall into the general tetracycline's characteristics, justifying the use of some data about tetracyclines.

Moderate to severe acne

Tetracyclines in general and lymecycline in particular have been used to treat acne. They may act by inhibiting propionibacteria, which reside in sebaceous follicles and metabolize lipids into

⁵ Present in <http://bestpractice.bmj.com/best-practice/monograph/958.html> on 08/04/2015

⁶ Present in <http://www.medscape.com/viewarticle/703256> on 08/04/2015

⁷ Present in <http://bestpractice.bmj.com/best-practice/monograph/608.html> on 08/04/2015

irritating free fatty acids. Tetracycline significantly reduced the overall grade, and the number of non-inflamed lesions, papules and pustules by the third month. It also reduced significantly the non-inflamed lesions and papules at the end of the second month. The results indicate that tetracycline is far superior to the zinc complex in patients with moderately severe acne. Different reports support the efficacy of lymecycline for the treatment of moderate to severe acne, even when compared to alternative tetracyclines and lymecycline has superior practicability compared with tetracycline due to the requirement for less frequent administration.

Acute sinusitis

Lymecycline may help to accelerate the healing process in the case of acute sinusitis. Also, it has been demonstrated that tetracycline and lymecycline can be found in concentrations that are sufficient to inhibit most pathogens found in the respiratory tract. In a clinical trial performed to evaluate the efficacy and the tolerance of lymecycline 2 x 300 mg/day in patients with subacute sinusitis, it was concluded that lymecycline can be considered a first choice antibiotic in the treatment of acute and subacute sinusitis.

Acute exacerbation of chronic bronchitis

Patients, most of whom were suffering from chronic bronchitis with purulent exacerbations, were treated with lymecycline 1600 mg (containing 1200 mg of tetracycline base) or with tetracycline hydrochloride 2 g daily. In this smaller dose lymecycline was equal to tetracycline hydrochloride in clinical effect and superior in tolerance. This practical superiority may well apply to patients with other illnesses where high doses of the tetracyclines are indicated, though advantages in tolerance may be less marked when a smaller dose is sufficient.

Helicobacter pylori infection

Rosacea is considered as polietiological dermatosis. *Helicobacter pylori* infection seems to be one of the etiopathogenetic factors due to dyspeptic complaints and digestive tract disorders in rosacea patients. Tetracycline and metronidazol have been used for years in rosacea therapy with good results. *Helicobacter pylori* was eradicated from digestive tract by those drugs which confirms its role in rosacea pathogenesis.

Urogenital infections caused by Chlamydia trachomatis

Men with non-gonococcal urethritis and their sexual partners were treated either with erythromycin stearate 500 mgx2 for 15 days or with lymecycline 300 mgx2 for 10 or 20 days. *Chlamydia trachomatis* was isolated from 40% of the men, from 26% of their female partners and from 56% of the partners of men with chlamydia-positive urethritis. The cure rate was 86-90% in men with chlamydia-positive and 89-100% in men with chlamydia-negative urethritis.

Soft tissue infection

Because of resistance, tetracyclines fell into disuse for infections caused by staphylococci, streptococci, or meningococci. However, community strains of methicillin-resistant *S. aureus* often are susceptible to tetracycline, doxycycline, or minocycline, which appear to be effective for uncomplicated skin and soft-tissue infections. Approximately 85% of strains of *S. pneumonia* are susceptible to tetracyclines, and doxycycline remains an effective agent for empirical therapy of community-acquired pneumonia.

VI.2.3 Unknowns relating to treatment benefits

N/A

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hypersensitivity	Lymecycline or its excipients may cause hypersensitivity reactions in patients.	[Product name] is contraindicated in case of hypersensitivity to the active substance or to any of the excipients. These conditions should be closely monitored.
<i>Clostridium difficile</i> -associated diarrhoea and pseudomembranous colitis	<p><i>Clostridium difficile</i>-associated diarrhoea and pseudomembranous colitis have been reported for [Product name].</p> <p>As with all antibiotics, overgrowth of non-susceptible organisms may cause candidiasis, pseudomembranous colitis (<i>Clostridium difficile</i> overgrowth), glossitis, stomatitis, vaginitis, or staphylococcal enterocolitis.</p>	<p>It is important to consider these diagnoses in patients who present with diarrhoea subsequent to the administration of [Product name]. In such circumstances, the use of supportive measures together with the administration of specific treatment for <i>Clostridium difficile</i> should be considered.</p> <p>If you get any side effects, talk to your doctor, pharmacist or nurse.</p>
Photosensitivity	Cutaneous phototoxicity is mainly associated with doxycycline, democlocycline, and chlortetracycline, and infrequent reports of phototoxicity to tetracycline, oxytetracycline and lymecycline have appeared. Lymecycline is metabolized to tetracycline. The clinical reports were supported by a double-blind	You should avoid direct exposure to sunlight, or artificial sunlight from sunbeds. If you experience skin discomfort, then stop taking this medicine and seek advice from your doctor.

Risk	What is known	Preventability
	crossover phototoxicity study of democlocycline, doxycycline, lymecycline, and placebo in which 2/8 subjects reacted to each lymecycline and democlocycline, and 7/8 subjects reacted to doxycycline.	
Benign intracranial hypertension when used concomitantly with systemic retinoids	The concomitant usage of oral retinoids should be avoided as this may increase the risk of benign intracranial hypertension.	[Product name] is contraindicated in case of concurrent treatment with oral retinoids and use in association with systemic retinoids.
Dental staining and enamel hypoplasia in the foetus or child when used during pregnancy, breast feeding or in use by children under 12 years old	<p>Tetracyclines in general cross the placenta and lymecycline in particular may cause adverse effects on fetus. Tetracyclines are selectively absorbed by developing bones and teeth and may cause dental staining and enamel hypoplasia. In addition these compounds readily cross the placental barrier and therefore this product should not be given to pregnant or lactating women.</p> <p>Dental dyschromia and/or enamel hypoplasia may occur if the product is administered in children younger than 8 years old.</p>	[Product name] is contraindicated during pregnancy, breast feeding and in children under 12 years old.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Emergence of bacterial resistance	Prolonged use of antibiotics may result in the appearance of resistant organisms and superinfections. Cross-resistance between tetracyclines may develop in micro-organisms, and similarly, cross-sensitisation in patients. The product should therefore be used with caution and especially the use should be considered.
Toxicity in patients with hepatic impairment	Lymecycline must be used with caution in patients with hepatic impairment, since there's potential for accumulation with increased toxicity.

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Emergence of bacterial resistance	Prolonged use of antibiotics may result in the appearance of resistant organisms and superinfections. Cross-resistance between tetracyclines may develop in micro-organisms, and similarly, cross-sensitisation in patients. The product should therefore be used with caution and especially the use should be considered.
	Hepatic toxicity typically develops in patients receiving 2g or more of drug per day parenterally, but this effect also may occur when large quantities are administered orally. Pregnant women are particularly susceptible to tetracycline-induced hepatic damage. Tetracyclines absolute contraindications are known severely impaired hepatic function.
Liver toxicity in patients with renal impairment	Lymecycline's principal route of elimination is via renal excretion, with some 25–30 % of the dose being excreted via the renal route, and biliary excretion also plays a role. The product must be used with caution in patients with renal impairment, since there's potential for accumulation with increased toxicity.
Exacerbation of systemic lupus erythematosus	In the study published by Cunliffe et al., a comparison of the efficacy and safety of lymecycline plus adapalene gel 0.1%, versus lymecycline plus gel vehicle was performed. Local cutaneous tolerance was generally good in both groups. Although more patients in the lymecycline plus adapalene group experienced erythema, dryness, scaling and stinging/burning sensations during the study.
Neuromuscular blockade when used in patients with myasthenia gravid	Lymecycline can cause weak neuromuscular blockade so should be used with caution in Myasthenia Gravis.

Missing information

Risk	What is known
None	

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations

for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimisation measures.

The summary of product characteristics and package leaflet for Lymecline 300 mg capsules, hard can be found in the national competent authority's website, once approved.

This medicine has no additional risk minimisation measures.

VI.2.6 *Planned post authorisation development plan*

Not applicable.

VI.2.7 *Summary of changes to the Risk Management Plan over time*

Not applicable, this is the first RMP.