VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Rapenin (phenoxymethylpenicillin potassium) is indicated for the treatment of infections caused by penicillin-sensitive bacteria. Bacterial infections are observed worldwide with no recognized racial or ethnic predispositions to infection. Bacterial infections may be observed in people of any age, although the prevalence of infection is higher in children, presumably because of the combination of multiple exposures (in school or daycare) and little immunity. A selection of common infections is presented below, since a complete description of all medical conditions treatable with Rapenin is not feasible to present in this context:

- Strep throat is a contagious disease caused by infection with streptococcal bacteria, most common in school-aged children and teens, with a peak incidence between 5 to 15 years of age. It is estimated that approximately 15% to 40% of cases of sore throat in this age group are caused by Streptococcus spp bacteria. Adults may also develop strep throat, though less commonly (accounts for approximately 5% to 10% of cases of sore throat). Strep throat most commonly occurs between late fall and early spring. It is more widespread during the school year when groups of students are present within an enclosed space (Doerr 2013). In rare cases, if not treated, strep throat can lead to rheumatic fever which can affect the heart several years later (Vorvick 2012).
- Pharyngitis is an inflammatory condition of the oropharynx. Group A Streptococcus (GAS) is the most common bacterial cause, responsible for 5%–15% of sore throat visits in adults and 20%–30% in children.
- Pneumonia is an inflammatory condition of the lung and often a bacterial infection that requires antibiotic treatment. In Europe, 1–10% of the population seek medical attention for lower respiratory tract infections and of those 10–15% has pneumonia. The yearly incidence of pneumonia has been estimated to 1% in Europe (Strålin 2008). The annual incidence rate in United Kingdom is 6/1000 in the 18–39 age group. This rises to 34/1000 in people aged 75 years and over. Admission to hospital is needed in 20–40% of patients with community acquired pneumonia. About 5–10% of these patients are admitted to intensive care. The overall mortality from community acquired pneumonia is 5–10% (Hoare 2006)
- Otitis media is an infection of the middle ear and eardrum caused by bacteria growing in the middle ear behind the eardrum. It is the most common infectious disease in young children, having occurred in 80% of all children by age 3. Furthermore, acute otitis media and otitis media with effusion are among the main reasons for early childhood consultations with general practitioners, and acute otitis media is one of the most common reasons for prescribing antibiotic treatment (Mortensen 2013). The incidence of acute otitis media is highest in the first 2 years of life and decreases to 2% by the age of 8 years. More than two thirds of children have suffered at least one attack of acute otitis media by their third birthday, and around half have experienced three or more episodes. Some of these patients develop tympanic effusion, which may result in middle ear hearing impairment persisting into later childhood (Thomas 2014).
- Cellulitis is a common infection of the skin and the tissues underneath the skin. People at risk for getting cellulitis include those with trauma to the skin or other medical problems such as diabetes, circulatory problems, liver disease and skin disorders such as eczema, psoriasis, or infectious diseases that cause skin lesions such as chickenpox or severe acne. Because cellulitis is not a reportable disease, the exact prevalence is uncertain; however, it is a relatively

common infection, affecting all racial and ethnic groups and antibiotic regimens are effective in more than 90% of patients. There is no statistically significant difference in the incidence of cellulitis in men and women, and no age predilection is usually described. A study of an insurance database found an incidence rate of 24.6 cases per 1000 person-years and in a large epidemiologic hospital-based study on skin, soft-tissue, bone, and joint infections, 37.3% patients were identified as having cellulitis. Furthermore, cellulitis was found to account for approximately 3% of emergency medical consultations at one United Kingdom district general hospital (Herchline 2014).

- Streptococcus pyogenes (group A streptococcus) is responsible for a diverse range of clinical manifestations, from mild skin/soft tissue infections and pharyngitis to more serious diseases, such as bacteremia, cellulitis, puerperal sepsis, meningitis, pneumonia, and necrotizing fasciitis. Development of streptococcal toxic shock syndrome (STSS) in these patients increases the risk of death substantially. Overall rates of reported infection varies, reaching 3/100,000 population in the northern European countries: Finland, 2.46; Denmark, 2.58; Sweden, 3.10; United Kingdom, 3.31 (Lamagni 2008).

VI.2.2 Summary of treatment benefits

The active substance in Rapenin, phenoxymethylpenicillin potassium, is a penicillin (antibacterial medicine) that prevents the bacteria from buildning a normal cell wall. Without cell walls, the bacteria die fast. Penicillins have been in clinical use for over 50 years. Penicillins are of very low toxicity when taken in overdose. Phenoxymethylpenicillin potassium, a natural penicillin, has been widely available as an orally available form of penicillin for over 50 years. The toxicity of phenoxymethylpenicillin is low and its side effect profile is well known and severe side effects are uncommon. Although the use of phenoxymethylpenicillin has become reduced due to the emergence of bacterial strains that are resistant, it is still a useful treatment for mild to moderate bacterial infections where the incidence of resistance to penicillins is known to be low.

Sore throats should only be treated with antibiotics if the strep test is positive. Penicillin or amoxicillin is usually first tried. Vorvick 2012). Accurate diagnosis of streptococcal pharyngitis followed by appropriate antimicrobial therapy is important for the prevention of acute rheumatic fever and for the prevention of suppurative complications, e.g. peritonsillar abscess, cervical lymphadenitis, mastoiditis, and, possibly, other invasive infections (Shulman 2012 and Vorvick 2012). Based on their narrow spectrum of activity, infrequency of adverse reactions, and modest cost, penicillin or amoxicillin is the recommended drug of choice for those non-allergic to these agents (Shulman 2012). Antibiotics are the only medications with demonstrated efficacy in the management of acute otitis media. The antibiotic chosen should cover most of the common bacterial pathogens and be individualized for the child with regard to allergy, tolerance, previous exposure to antibiotics, cost, and community resistance levels. Duration of treatment may also be a consideration in the choice of antibiotic (Donaldson 2014).

Phenoxymethylpenicillin has been used in the treatment of neonates, and no special precautions are necessary. Phenoxymethylpenicillin has been extensively used for treatment of infection in children. Phenoxymethylpenicillin can be used during pregnancy and breast-feeding. There are no special problems relating to the use of penicillin in elderly patients. Phenoxymethylpenicillin can be used safely in patients with hepatic dysfunction without dose modification. Elimination is delayed in patients with renal dysfunction and a modest dose reduction may be appropriate in patients with severe renal failure.

VI.2.3 Unknowns relating to treatment benefits

The sometimes rapid induction of antbiotics resistance in bacterial strains may result in low treatment efficiency of a previously treatable infection.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Allergic reactions e.g. anaphylactic shock, angiooedema	In a small number of patients penicillin can cause allergic reactions and anaphylactic shock. Phenoxymethylpenicillin may also be cross-allergenic with other penicillins and may cause anaphylactic shock in the absence of a past history of allergy to phenoxymethylpenicillin. Risk populations include patients with asthma and other significant allergic syndromes.	Testing for sensitivity effectively show if the patient is in danger to develop reaction to phenoxymethylpenicillin. Phenoxymethylpenicillin should be used with causion in patients with histories of allergic diseases or asthma bronchiale. If the patient develops an allergic reaction, the treatment should be discontinued immediately and treatment with epinephrine, antihistamine and corticosteroids should be initiated.
Cross-allergy between penicillins and cepahalosporins	Phenoxymethylpenicillin may also be cross-allergenic with cephalosporines and may cause anaphylactic shock in the absence of a past history of allergy to phenoxymethylpenicillin. Risk populations include patients with asthma and other significant allergic syndromes.	Testing for sensitivity effectively show if the patient is in danger to develop reaction to phenoxymethylpenicillin. Phenoxymethylpenicillin should be used with causion in patients with histories of allergic diseases or asthma bronchiale. If the patient develops an allergic reaction, the treatment should be discontinued immediately and treatment with epinephrine, antihistamine and corticosteroids should be initiated.
Colitis and pseudomembranous colitis	Pseudomembranous colitis is an infection disease of the colon most commonly caused by *Clostridium difficile* and results	Discontinuation of antibiotic may cure the disease, otherwise administration of antibiotics effective against *Clostridium*

Risk	What is known	Preventability
	in diarrhoea, sometimes bloody, abdominal pain and fever. It is almost always a result of antibiotic treatment including phenoxymethylpenicillin.	*difficile* is an alternative.
Interaction with methotrexate	Administration of phenoxymethylpenicillin during methotrexate treatment can cause increased toxicity of methotrexate.	Frequent monitoring of the patient and dose adjustment of methotrexate may prevent the methotrexate induced toxicity.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
None	NA

Missing information

Risk	What is known
None	NA

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) 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 (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Rapenin can be found on the authority's web page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

NA

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	At time of authorisation 01/11/2012	Identified Risks: *Allergic reactions*	
2.0	03/03/2014	*Colitis and*	Two safety concerns added.

Version	Date	Safety Concerns	Comment
		pseudomembranous colitis added as an identified risk. *Interaction with methotrexate* added as an identified risk.	Change to new RMP template.
3.0		*Allergic reactions e.g. anaphylactic shock, angiooedema* *Cross-allergy between penicillins and cepahalosporins*	"Allergic reactions" expanded and identified risk of cross-allergy between penicillins and cepahalosporins listed.