VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Pneumococcal infection is a major cause of morbidity and mortality worldwide. In 2005, WHO estimated that 1.6 million deaths were caused by this agent annually; this estimate included the deaths of 0.7–1 million children aged under 5 years. Most of these deaths occurred in poor countries and included a disproportionate number of children under the age of 2 years. In Europe and the USA, S. pneumoniae is the most common cause of community-acquired bacterial pneumonia in adults. Where the annual incidence ranges from 10 to 100 cases per 100 000 population[1].

S. aureus is the most frequently occurring bacterial pathogen among clinical isolates from hospital inpatients in the United States and is the second most prevalent bacterial pathogen among clinical isolates from outpatients.[2].

Streptococcus pyogenes diseases have increased globally over the past 2 decades. To examinethe epidemiological patterns of these diseases within Europe, data were collected through a European Union FP-5-funded program (Strep-EURO). Prospective population-based surveillance of severe S. pyogenes infection diagnosed during 2003 and 2004 was undertaken in Cyprus, the Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Romania, Sweden, and the United Kingdomusingastandardized case definition. A total of 5,522 cases were identified during this period. Rates of reported infection varied, reaching 3/100,000 population in the northern European countries. Seasonal patterns of infection showed remarkable congruence between countries. The risk of infection was highest among the elderly, and rates were higher in males than in females in most countries. The findings from Strep-EURO confirm a high incidence of severe S. pyogenes disease in Europe[3].

VI.2.2 Summary of treatment benefits

Penicillin V potassium tablets for oral are used in the treatment of mild to moderately severe infections due to penicillin G-sensitive microorganisms.

No additional studies were conducted as Phenoxymethylpenicillin Aurobindo is a generic medicine that is given by parentral and contains the same active substance as the reference medicine.

Because Phenoxymethylpenicillin Aurobindo is a generic, its beneficial treatment effects are taken as being the same as the reference medicine’s.

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[1]http://www.who.int/ith/diseases/pneumococcal/en/.

[2] Christoph K. Nabera,Staphylococcus aureus Bacteremia: Epidemiology, Pathophysiology, and Management StrategiesOxford JournalsMedicine Clinical Infectious Diseases Volume 48, Issue Supplement 4Pp. S231-S23

[3] Theresa L. Lamagni, Jessica Darenberg, Epidemiology of Severe Streptococcus pyogenes Disease in Europe, journal of clinical microbiology, July 2008, p. 2359–2367

VI.2.3 Unknowns relating to treatment benefits

There are no unknowns relating to treatment benefits that the MAH is aware of.

VI.2.4 Summary of safety concerns

Risk	What is known	Preventability
Important identified risks		
Hypersensitivity reactions (allergic reaction / anaphylactoid reactions)	Hypersensitivity to phenoxymethylpenicillin, other penicillins or to any of the excipients listed in section . 6.1. Cross allergy between penicillins and cephalosporins occur. If the patient develops an allergic reaction, the treatment should be stopped immediately, and treatment with epinephrine, antihistamine and corticosteroid therapy.	Physician supervision andCare.
Antibiotic-induced pseudomembranous colitis	Diarrhoea / pseudomembranous colitis caused by Clostridium difficile occurs. On suspicion of pseudomembranous colitis treatment must be discontinued immediately and appropriate antibiotic therapy.	Physician supervision andCare.
Erythema multiforme	Skin and subcutaneous tissue disorders Uncommon: Urticaria, angioedema, erythema multiforme, exfoliative dermatitis	Phenoxymethypenicillin mustbe discontinued immediately and appropriate medical therapy instituted.
Non enzymatic urinary glucose testing may be false-positive	Non- enzymatic glucose urine test , and urobilinogen test with ninhydrin tests for the quantitative determination of the amino acid content of the urine may be false-positive using phenoxymethylpencillin.	During therapy with phenoxymethypenicillind etermination of glucose in urine should be carried out enzymatically.
Concomitant use of bacteriostatic antibiotics	Phenoxymethylpenicillin should not be combined with bacteriostatic chemotherapeutics / antibiotics	Concomitant administration of these drugs with Phenoxymethylpenicillin

	(e.g..Tetracyclines, sulfonamides and chloramphenicol), as this could possibly result in an antagonistic effect	should be avoided.
Haemolytic anaemia, leucopenia, thrombocytopenia, agranulocytosis	Blood and lymphatic system disorders: Very rare: Hemolytic anemia, leukopenia , thrombocytopenia, agranulocytosis	Physician supervision and Care.
Effects on laboratory tests	Non- enzymatic glucose urine test , and urobilinogen test with ninhydrin tests for the quantitative determination of the amino acid content of the urine may be false-positive using phenoxymethylpencillin .	Physician supervision and Care.
Concomitant use of uricosuric drugs (e.g. probenecid)	Probenecid decreases the renal tubular secretion and increases serum concentrations of penicillin.	Physician supervision and Care.
Concomitant use with methotrexate	Co-administration of methotrexate and phenoxymethylpenicillin should be done with caution since it may lead to increased toxicity of methotrexate. Close monitoring of the patient may be necessary.	Physician supervision and Care.
Drug Resistance	The resistance may occur due to bacterial synthesis of large numbers of beta-lactamases that hydrolyze penicillin . Several of these may be inhibited by clavulanic acid. In addition, the resistance may occur due to the production of altered penicillin-binding proteins (PBPs) . The resistance mediated by plasmids often . Cross-resistance occurs in betalaktamgruppen(penicillins and cephalosporins). Resistance situation varies geographically, and information on local resistance patterns should be obtained from the microbiology	Physician supervision andCare.

	laboratory.	
Positive direct Coombs'	There have been reports of positive direct Coombs'test with phenoxymethypenicillin.	Physician supervision andgauidance.
Important potential risks		
None		
Missing information		
None		

VI.2.5 Summary of additional risk minimisation measures by safety concern

Not applicable

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Not applicable

Studies which are a condition of the marketing authorisation

None.

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
2.0	29 September 2014	Version 1.0 is amended as per the preliminary assessment report received from Denmark for safety specification. The following important identified risks are deleted: – Use in patients with a gastrointestinal disease – Use in long-term treatment – Use in patients on potassium -restricted diet – Use in patients with allergic diseases or bronchial asthma – Use in pregnancy and lactation The following important identified risks are added: – Erythema multiforme – Non enzymatic urinary	RMP has been updated as per the assessor comments.

Version	Date	Safety Concerns	Comment
		glucose testing may be false-positive – Concomitant use of bacteriostatic antibiotics – Haemolytic anaemia, leucopenia, thrombocytopenia, agranulocytosis – Positive direct coombs test	