VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Pivmecillinam LEO 400 mg film-coated tablets is an antibiotic indicated for the treatment of acute uncomplicated cystitis (bladder infection) in adults, adolescents and children > 6 years and weighing > 30 kg.

Urinary tract infections are very common; in the US nearly 7 million patients sought medical treatment because of urinary tract infections in 1997, including 2 million cases of bladder infection. In Europe, such data is not available, but data obtained from the USA can be applied with caution to the European situation.

Women are more likely to get urinary tract infections than men. Nearly one in three women will have had at least one urinary tract infection requiring antibiotic treatment by the age of 24 years. Almost half of all women will experience a urinary tract infection during their lifetime.

Infants, pregnant women, the elderly and patients with spinal cord injuries, catheters, diabetes, multiple sclerosis, AIDS, HIV or with abnormalities in the urinary system are more likely to get urinary tract infections. In elderly, urinary tract infections are the second most common form of infection, accounting for nearly 25% of all infections. Urinary tract infections in patients with catheters is the most common hospital-acquired infection, accounting for >1 million cases in hospitals and nursing homes in the US yearly.

Urinary tract infections are bothersome with urinary symptoms that can lead to work absence and decreased ability to engage in activities of daily living. Children with bladder infection are usually without fever and in good general health, but frequently experience urinary problems. However, complicated urinary tract infections may lead to sepsis and death, especially in frail elderly and in those with urinary incontinence where urinary tract infection may be related to skin damage and open wounds.

VI.2.2 Summary of treatment benefits

Bladder infections are treated with antibiotics. Besides pivmecillinam, fosfomycin and nitrofurantoin are considered as drugs of first choice in many countries in Europe, when available. Cotrimoxazole and trimethoprim should only be considered as drugs of first choice in areas with known resistance rates for E. coli of < 20%.

VI.2.3 Unknowns relating to treatment benefits

Pivmecillinam film-coated tablets have been on the market for more than 30 years. There is no evidence to suggest that the pivmecillinam film-coated tablets are not equally effective in all patient groups.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Carnitine depletion	Carnitine is required to produce energy from fat in the cells of the body. Too low carnitine levels may result from different reasons, i.e., genetic disorders, too low intake or increased use of carnitine in the body. Carnitine depletion may cause a variety of disorders including muscle, liver and cardiac disease and may be fatal in children if not treated in due time. It is known that pivmecillinam may cause reduction of the body carnitine storage. Carnitine binds to a part of the pivmecillinam and is lost via the urine. After a few days of treatment carnitine in serum is reduced to about 50% of the initial values. Depletion of the carnitine stored in the muscle to 50% of initial value takes about 50 days. The use of pivmecillinam in patients with existing carnitine deficiency or disorder may thus increase the risk of carnitine depletion and clinical symptoms.	Pivmecillinam LEO 400 mg film-coated tablets SmPCs should contain a contraindication for use in patients with genetic metabolism anomalies like carnitine transporter defect or organic acidurias, such as methylmalonic aciduria or propionic acidaemia. Furthermore, a warning that long-term use increases the risk of carnitine deficiency should be included in the SmPCs. Finally, in section 4.5 of the SmPCs it should be stated that concurrent treatment with valproic acid, valproate or other medication liberating pivalic acid should be avoided.
Cross-hypersensitivity with penicillins and cephalosporins	If a person has experienced an allergic reaction to another penicillin or a cephalosporin there is an increased risk that use of pivmecillinam will also result in a hypersensitivity reaction.	Pivmecillinam LEO 400 mg film-coated tablets SmPCs should contain a contraindication for use in patients with a known hypersensitivity to penicillins or cephalosporins.

Important potential risks

Risk	What is known	Preventability
Pseudomembranous colitis	Treatment with an antibiotic may affect the normal bacterial flora in the colon, and colonisation with the bacteria *Clostridum difficile* may occur. The bacteria release toxins which may result in diarrhoea and inflammation of the colon (colitis). When adherent yellow or white plaques, pseudomembranes, are present on the intestinal mucosa the disease is called pseudomembranous colitis.	Pivmecillinam LEO 400 mg film-coated tablets SmPCs should contain a warning that Pseudomembranous colitis caused by *Clostridum difficile* may occur and that in case of diarrhoea the possibility of pseudomembranous colitis should be considered and appropriate precaution taken.

Important missing information

Not applicable.

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 Pivmecillinam LEO 400 mg film-coated tablets can be found in the EPAR page for Pivmecillinam LEO 400 mg film-coated tablets.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post authorisation studies or development are planned at this point.

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

Not applicable as this is the first RMP for this product.