CONFIDENTIAL

Pivmecillinam LEO (Selexid®) 400 mg film-coated tablets
EU – Risk Management Plan

LEO Pharma A/S
Global Pharmacovigilance

Version: 1.0
Date: 28-Feb-2014

Active substance(s) (INN or common name):	Pivmecillinam
Pharmaco-therapeutic group (ATC Code):	J01CA08
Name of Marketing Authorisation Holder or Applicant:	LEO Pharma A/S Industriparken 55 DK - 2750 Ballerup
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Pivmecillinam hydrochloride 400 mg film-coated tablets (Pivmecillinam LEO, Selexid®, Selexid® LEO)

Data lock point for this RMP	30-Apr-2013
Version number	1.0
Date of final sign off	28-Feb-2014

Table of Contents

Part I: Product(s) Overview

Administrative information on the RMP

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
Part II Safety Specification	SI Epidemiology of the indication and target population(s)	Not applicable	Not applicable
	SII Non-clinical part of the safety specification	Not applicable	Not applicable
	SIII Clinical trial exposure	Not applicable	Not applicable
	SIV Populations not studied in clinical trials	Not applicable	Not applicable
	SV Post-authorisation experience	Not applicable	Not applicable
	SVI Additional EU requirements for the safety specification	Not applicable	Not applicable
	SVII Identified and potential risks	Not applicable	Not applicable
	SVIII Summary of the safety concerns	Not applicable	Not applicable
Part III Pharmacovigilance Plan		Not applicable	Not applicable
Part IV Plan for post-authorisation efficacy studies		Not applicable	Not applicable
Part V Risk Minimisation Measures		Not applicable	Not applicable

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
Part VI Summary of RMP		Not applicable	Not applicable
Part VII Annexes	ANNEX 2 Current or proposed SmPC/PIL	Not applicable	Not applicable
	ANNEX 3 Worldwide marketing status by country	Not applicable	Not applicable
	ANNEX 4 Synopsis of clinical trial programme	Not applicable	Not applicable
	ANNEX 5 Synopsis of pharmaco-epidemiological study programme	Not applicable	Not applicable
	ANNEX 6 Protocols for proposed and on-going studies in Part III	Not applicable	Not applicable
	ANNEX 7 Specific adverse event follow-up forms	Not applicable	Not applicable
	ANNEX 8 Protocols for studies in Part IV	Not applicable	Not applicable
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	Not applicable	Not applicable
	ANNEX 10 Details of proposed additional risk minimisation activities	Not applicable	Not applicable
	ANNEX 11 Mock up examples	Not applicable	Not applicable
	ANNEX 12 Other supporting data	Not applicable	Not applicable

* A new RMP version number should be assigned each time any Parts/modules are updated.
Some modules of the RMP may be omitted (for eligible types of products see GVP V table V.2) if the RMP relates only to products falling into these categories. In these circumstances leave the date field blank and write "Not applicable" or "NA" in the version field.

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Overview of versions:

Version number of last agreed RMP:

Version number	No approved versions
Agreed within	No approved versions

Current RMP versions under evaluation:

RMP Version number	Submitted on	Submitted within
No other versions are under evaluation	Not applicable	Not applicable

Invented name(s) in the European Economic Area (EEA)	Pivmecillinam LEO 400 mg film-coated tablets (DK) Selexid® 400 mg film-coated tablets (BE, ES, LU, NL) X-SYSTO® 400 mg film-coated tablets (DE, IT, PL)
Authorisation procedure	Decentralised procedure (DCP)
Brief description of the product including: Chemical class Summary of mode of action Important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines)	Chemical class: beta-lactam antibacterials, penicillins with extended spectrum. Pivmecillinam is the pivaloyloxymethyl ester of mecillinam. Pivmecillinam is rapidly absorbed from the gastrointestinal tract and hydrolysed to the active drug mecillinam. Mecillinam is active against a range of Gram-negative bacteria, in particular Enterobacteriaceae including *E. coli, Enterobacter, Klebsiella, Salmonella* and *Shigella spp*. The susceptibility of *Proteus* spp. varies. Mecillinam interferes with the biosynthesis of the bacterial cell wall but the target of the inhibition is different from other penicillins and cephalosporins. Mecillinam binds almost exclusively to Penicillin-Binding Protein 2 (PBP-2) whereas other penicillins and cephalosporins bind to PBP-1 and PBP-3. Pivmecillinam is the recommended INN; amdinocillin pivoxil is the USAN.
Indication(s) in the EEA	Acute uncomplicated cystitis
Posology and route of administration in the EEA	Generally, the official recommendations in each market on the appropriate use of antibiotics should be taken into account. For adults the recommended dose is 400 mg 2-3 times daily. No dose adjustment is necessary for the elderly, patients with reduced kidney function or hepatic impairment. For children above 6 years and weighing more than 30 kg the recommended daily dose is 20-40 mg/kg/day divided into 3 doses. The recommended duration of treatment is 3-7 days. Route of administration: oral. Pivmecillinam LEO 400 mg film-coated tablets must be taken with at least half a glass of liquid and may be taken with food.
Pharmaceutical form(s) and strengths	Film-coated tablets 400 mg

Country and date of first authorisation worldwide	NA	NA
Country and date of first launch worldwide	NA	NA
Country and date of first authorisation in the EEA	NA	NA

Is the product subject to additional monitoring in the EU? Yes ___ No_X_

Part II: Module SI - Epidemiology of the indication(s) and target population

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

SI.1 Epidemiology of the disease

Urinary tract infections (UTI), such as acute uncomplicated cystitis, are among the most prevalent infectious diseases (1). In Europe, there are no relevant data concerning the prevalence of various types of UTIs, including cystitis, and their impact on the quality of life of the affected population or socioeconomic costs (1). Data obtained from other countries and societies, e.g. the USA, can only be applied with caution to the European situation. According to the 1997 National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey, UTI accounted for nearly 7 million office visits, including more than 2 million visits for cystitis (2). Nevertheless, it is difficult to accurately assess the incidence of UTIs, because they are not reportable diseases in the United States. This situation is further complicated by the fact that accurate diagnosis depends on both the presence of symptoms and a positive urine culture, although in most outpatient settings this diagnosis is made without the verification by urine culture.

Women are significantly more likely to experience UTI than men. Nearly 1 in 3 women will have had at least 1 episode of UTI requiring antimicrobial therapy by the age of 24 years. Almost half of all women will experience a UTI during their lifetime (2). In children, UTI are among the most common bacterial infections and affect 2-3% of boys and 7-11% of girls in age 0-16 years (3). In non-institutionalized elderly populations, UTI is the second most common form of infection, accounting for nearly 25% of all infections (2).

Specific subpopulations at increased risk of UTI include infants, pregnant women, the elderly, patients with spinal cord injuries and/or catheters, patients with diabetes or multiple sclerosis, patients with acquired immunodeficiency syndrome (AIDS)/human immunodeficiency virus (HIV), and patients with underlying urologic abnormalities. Catheter-associated UTI is the most common nosocomial infection, accounting for >1 million cases in hospitals and nursing homes yearly. The risk of UTI increases with increasing duration of catheterization (2).

Besides pivmecillinam, fosfomycin and nitrofurantoin are considered as drugs of first choice for acute uncomplicated cystitis 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% (1).

UTI may be associated with significant morbidity and even mortality (4), but acute uncomplicated cystitis in the nonobstructed, adult, nonpregnant woman is believed to be a benign illness with no long-term medical sequelae (2). UTI is associated with bothersome urinary symptoms that can lead to work absence and decreased ability to engage in activities of daily living (4). Children with cystitis are usually without fever and in good general condition, but frequently experience urinary problems (3, 5).

SI.2 Concomitant medication(s) in the target population

According to the "Guidelines on Urological Infections" (1) there is no recommendation on any concomitant medication to antibiotics in the treatment of UTI. However, it is possible that prophylactic treatment may be continued during treatment of an active UTI. Cranberry products are recommended for prophylaxis of cystitis and co-administration with Pivmecillinam LEO 400 mg film-coated tablets may be expected in some patients (1). Prophylaxis by immune-active products like *E. Coli* bacterial extract OM-89 (Uro-Vaxomâ) is considered sufficiently well documented and has been recommended for immune-prophylaxis in female patients with recurrent uncomplicated UTI and co-administration may be expected (1). Accessibility of clinically proven probiotics for UTI prophylaxis is currently not universal but may also be considered. Furthermore, cystitis may be associated with pain and concomitant treatment with analgesics may be expected.

As UTIs are among the most prevalent infectious diseases (1), the possible concomitant medicines used in this group for other conditions are wide ranging.

SI.3 Important co-morbidities found in the target population

Patients with spinal cord injuries and/or catheters, patients with diabetes or multiple sclerosis, patients with AIDS/HIV, and patients with underlying urologic abnormalities are particularly at risk of developing UTI (2). Patients with these co-morbidities are not considered at increased risk when treated with Pivmecillinam LEO 400 mg film-coated tablets.

Based on the high number of patients experiencing cystitis the group of co-morbid diseases in which Pivmecillinam LEO 400 mg film-coated tablets can be used is wide-ranging.

SI.4 Reference list

1. Grabe M, Bjerklund-Johansen TE, Çek M, Naber KG, Tenke P, Wagenlehner F. Guidelines on Urological Infections. Apr-2010. European Association of Urology 2010. (eDoc no. 00361025)
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Part II: Module SII - Non-clinical part of the safety specification

According to the Guideline on Good Pharmacovigilance Practices – Module V Risk Management Plans, for new Marketing Authorization applications under Article 10(1) of Directive 2001/83/EC, RMP module SII may be omitted.

Part II: Module SIII - Clinical trial exposure

According to the Guideline on Good Pharmacovigilance Practices – Module V Risk Management Plans, for new Marketing Authorization applications under Article 10(1) of Directive 2001/83/EC, RMP module SIII may be omitted.

Part II: Module SIV - Populations not studied in clinical trials

According to the Guideline on Good Pharmacovigilance Practices – Module V Risk Management Plans, for new Marketing Authorization applications under Article 10(1) of Directive 2001/83/EC, RMP module SIV may be omitted.

Part II: Module SV - Post-authorisation experience

SV.1 Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons

Since the first MA for the originator product Selexid® was obtained in 1977 only one safety related regulatory action has been undertaken:

Based on results showing that the treatment with antibiotics containing pivalic acid e.g. pivmecillinam induces a reduction in the total body pool of carnitine (1), regulatory authorities/LEO Pharma A/S initiated changes to the originator product labelling world-wide to include recommendations concerning carnitine depletion in section 4.3, 4.4 and 4.8 in the SmPC.

Carnitine depletion is included as an important identified risk for Pivmecillinam LEO 400 mg film-coated tablets.

SV.2 Non-study post-authorisation exposure

SV.2.1 Method used to calculate exposure

The originator product Selexid® tablets was first launched in the United Kingdom in 1977. The actual total non-study post-authorisation usage data is best described in number of treatment courses, based on realised product volumes. An estimate of the number of patients exposed to Selexid® tablets is based on the total sales volume realised from LEO Pharma A/S to LEO affiliates, distributors, etc. held in the LEO Performance Management (LPM) system. The LPM system contains data dating back to 1st January 2001.

The following assumptions have been made:

An average treatment course with Selexid® tablets is estimated to be 600 mg per day for 6 days or 1200 mg per day for 3 days. This is equivalent to an estimated average treatment course of 3.6 g.

SV.2.2 Exposure

The total sales volume of tablets in the period 1-Jan-2001 to 30-Apr-2013: Approximately 64,4 ton. This corresponds to 17.9 million treatment courses, giving an average of 1.45 million exposed patients per year (17.9 million treatment courses /12.33 years).

Detailed data on exposure in different populations including the paediatric populations and divided on the different indications is not available retrospectively.

SV.3 Post-authorisation use in populations not studied in clinical trials

According to Guideline on Good Pharmacovigilance Practices – Module V Risk Management Plans patient groups identified in module SIV as having no or limited exposure should be discussed here. However, for a new MA application under Article 10(1) of Directive 2001/83/EC, RMP module SIV can be omitted and thus no such groups have been identified.

SV.4 Post-authorisation off-label use

Post-authorisation six reports of off-label use have been identified in the safety database for the originator product Selexid® (cumulative search until 30-Apr-2013); all were medically confirmed.

An analysis of the cases shows two reasons for the off-label use reported. In three cases (case nos. 105951, 108059 and 218537) Selexid® was used as prophylaxis rather than treatment and three cases (case nos. 212785, 213013, 216094) concerned long term use.

Only one case was considered serious. In this case (case no. 108059) abdominal pain was reported in a 30-year-old woman using Selexid® off-label as prophylaxis for recurrent urinary tract infections.

Additionally one non-serious case (case no. 105951) reported an adverse event other than off-label use; haematuria was reported in a 6-year-old child who received off-label prophylactic treatment with Selexid® for UTI. The reporter assessed the case as “probably not related” to pivmecillinam.

The remaining four cases reported no events other than off-label use (case nos. 212785, 213013, 216094 and 218537).

To sum up, two adverse events were reported in connection with off-label use, both in relation to prophylactic use of Selexid®. In the serious case no. 108059 the event abdominal pain was assessed as labelled. In case no. 105951 the haematuria reported was considered non-serious and unlabelled.

These few cases of off-label use are considered not to affect the risk benefit balance of Pivmecillinam LEO 400 mg film-coated tablets.

SV.5 Epidemiological study exposure

In 2002 – 2003, LEO Pharma A/S sponsored a population-based observational study of the use of the originator product Selexid® tablets in pregnancy. The study was conducted by the Department of Clinical Epidemiology at the University of Aarhus and a final report was submitted in 2004. The study was conducted in a county in Denmark with a population of approximately 500,000. Data regarding birth defects were obtained from the Danish Birth Registry and the county's Hospital Discharge Registry. Risk of miscarriage was investigated with two case-control designs in the same study based and focused on women who were hospitalized. Pivmecillinam use was estimated from pharmacy electronic accounting systems that are used to secure reimbursement from the National Health Service. Case control and cohort analyses were conducted. The study found that maternal use of pivmecillinam was not associated with birth defects, neonatal hypoglycaemia, respiratory distress syndrome, low Apgar score, preterm delivery, low birth weight or stillbirth. There were suggestions of an increased risk of miscarriage after the use of pivmecillinam but a causal relationship was not established (2, 3).

Additionally, studies not sponsored by LEO Pharma have been conducted. Several epidemiological studies have analysed the prevalence, antimicrobial susceptibility and resistance of pathogens in uncomplicated cystitis. In these studies (4-14), antibiotic resistance in bacteria from urine was analysed by ex vivo techniques. They did not investigate clinical exposure to pivmecillinam and are therefore not further discussed in this section.

In diagnosis-prescribing surveys in 2000, 2002 and 2005 in Swedish general practice, consultations, diagnosis, diagnostics and treatment choices were studied. For lower urinary tract infections there was a significant change in choice of prescribed antibiotics with an increase for pivmecillinam and nitrofurantoin and a decrease for trimethoprim, in accordance with current recommendations by the Swedish strategic programme against antibiotic resistance (STRAMA) (15). The prescribing of pivmecillinam increased significantly from 2002 (31%, 95% CI 27-35) to 2005 (51%, 95% CI 46-55).

In another study, antibiotic prescribing in general practice was compared between Italy (Ravenna) and Denmark (Funen). Pivmecillinam represented 3.1% of the defined daily doses

(DDD) prescribed in Funen, Denmark whereas it was not included in the antibiotics making up 90 % of total DDD prescribed in Ravenna, Italy (16).

SV.6 Reference list

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2. Norgaard M, Skriver MV, Sorensen HT, Schonheyder HC, Pedersen L. Risk of miscarriage for pregnant users of pivmecillinam: a population-based case-control study. APMIS. 2008;116(4):278-83. (eDoc no. 00361052)
3. Skriver MV, Norgaard M, Pedersen L, Schonheyder HC, Schonheyder HC. Pivmecillinam and Adverse Birth and Neonatal Outcomes: A Population-based Cohort Study. Scand J Infect Dis. 2004;36(10):733-7. (eDoc no. 00361051)
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8. Kamenski G, Wagner G, Zehetmayer S, Fink W, Spiegel W, Hoffmann K. Antibacterial resistances in uncomplicated urinary tract infections in women: ECO.SENS II data from primary health care in Austria. BMC.Infect.Dis. 2012;12(1):222. (eDoc no. 00361046)

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11. Naber KG, Schito G, Botto H, Palou J, Mazzei T. Surveillance study in Europe and Brazil on clinical aspects and Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC): implications for empiric therapy. Eur.Urol. 2008;54(5):1164-75. (eDoc no. 00361043)

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16. Vaccheri A, Bjerrum L, Resi D, Bergman U, Montanaro N. Antibiotic prescribing in general practice: striking differences between Italy (Ravenna) and Denmark (Funen). J Antimicrob.Chemother. 2002;50(6):989-97. (eDoc no. 00361041)

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for harm from overdose

For Pivmecillinam LEO 400 mg film-coated tablets the recommended dose for adults is 400 mg 2-3 times daily. For children above 6 years and weighing more than 30 kg the recommended daily dose is 20-40 mg/kg/day divided into 3 doses. The recommended duration of treatment is 3-7 days.

For the originator product Selexid® tablets dosages of up to 2,400 mg a day for adults and children above 6 years (weighing more than 20 kg) and up to 60 mg/kg/day for younger children have been approved in EU.

Post authorisation no reports of overdose have been identified in the safety database for the originator product Selexid® (cumulative search until 30-Apr-2013).

A search in PubMed (on the 04-Jun-2013) on the terms Selexid, pivmecillinam or mecillinam and overdose returns no hits. Furthermore, no information on potential overdose with pivmecillinam or mecillinam was found in the scientific sources DrugDex (1, 2) or Martindale (3, 4). For penicillins it is stated in Poisindex (5) that nausea, vomiting and diarrhoea may develop with ingestion and that agitation, confusion, stupor, coma, hallucinations, multifocal myoclonus, seizures and encephalopathy may occur following massive doses of IV penicillins.

Based on the lack of reported cases of overdose post marketing and the lack of literature concerning this, the risk of harm from overdose is assessed as very low.

SVI.2 Potential for transmission of infectious agents

The potential for transmission of an infectious agent is very low. Pivmecillinam LEO 400 mg film-coated tablets indicated for oral use is a pharmaceutical product produced according to GMP. It does not contain any biological substances of human origin. Drug substances and excipients are supplied with the appropriate compliance certification.

SVI.3 Potential for misuse for illegal purposes

Pivmecillinam LEO 400 mg film-coated tablets will be available as a prescription medicine and the availability in the market is therefore limited. Pivmecillinam LEO 400 mg film-coated tablets is not associated with mood-altering, psycho-active or addictive properties or other properties that would promote illegal use.

The potential and interest for misuse for illegal purposes is therefore assessed as negligible.

SVI.4 Potential for medication errors

Pivmecillinam LEO 400 mg film-coated tablets is supplied as film coated tables for oral ingestion. Post-marketing (cumulative search in the safety database until 30-Apr-2013) no adverse events connected to medication errors have been reported for the originator product Selexid®. The potential for medication errors is therefore assessed as negligible.

SVI.4.1 Description of medication errors during the clinical trial programme

Not applicable.

SVI.4.2 Preventive measures for the final product(s) being marketed

Not applicable.

SVI.4.3 Effect of device failure

Not applicable.

SVI.4.4 Reports of medication errors with the marketed product(s)

Pivmecillinam LEO 400 mg film-coated tablets will be available as film-coated tables for oral ingestion. Post-marketing (cumulative search in the safety database until 30-Apr-2013) no adverse events connected to medication errors have been reported for the originator product Selexid®. The potential for medication errors is therefore assessed as negligible.

SVI.5 Potential for off-label use

The risk associated with off-label use is low. The proposed indication is for a well-recognised medical condition and Pivmecillinam LEO 400 mg film-coated tablets will be a prescription medicine in Europe. The post-authorisation off-label use of the originator product Selexid® is discussed in module SV4, and long-term use in children is discussed in module SVI.6 below. To sum up, only six reports of off-label use have been received cumulatively. The potential for off-label use of Pivmecillinam LEO 400 mg film-coated tablets is assessed as negligible.

SVI.6 Specific Paediatric issues

Pivmecillinam has been evaluated in children for treatment of acute urinary tract infections (6-11). An additional study (12) enrolled subjects aged 15 – 55 years. These studies report outcomes in children consistent with those reported in adult women and, in the one comparative trial, similar efficacy of pivmecillinam and sulfamethoxazole. Reported adverse effects were infrequent, mild, and similar to those reported for sulfamethoxazole.

Several clinical trials evaluate long term use of pivmecillinam in children. Barclay (8) gave pivmecillinam 200 mg orally once daily to 21 children for up to 12 months for prophylaxis of urinary infection. Ten of 12 children treated for over 3 months remained free of bacteriuria for one year. Carlsen (13) reported that pivmecillinam (100 mg/day < 6 years; 200 mg/day ≥ 6 years) was as effective as and significantly better tolerated than nitrofurantoin given for 6 – 10 months to 35 children with vesicouretric reflux and recurrent urinary infection. An open study (10) enrolled 20 girls with recurrent bacteriuria who received pivmecillinam 5 – 10 mg/kg at bedtime for a total of 228 months. One 16-year-old girl discontinued treatment at 3 weeks due to complaints of vaginal discharge, but no other side effects were reported.

Overall, these studies have shown that the safety and efficacy profile of pivmecillinam in children is similar to that of adults.

SVI.6.1 Issues identified in paediatric investigation plans

Not applicable.

SVI.6.2 Potential for paediatric off-label use

Not applicable.

SVI.7 Conclusions

No safety concerns have been identified in module SVI to be carried through to module SVII identified and potential risk.

SVI.8 Reference list

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3. Martindale Pivmecillinam hydrochloride. Lexicomp - Martindale: The Complete Drug On-line access on the 07-Nov-2012. (eDoc no. 00361758)
4. Martindale Mecillinam. Lexicomp - Martindale. The Complete Drug Reference. On-line access on the 27-May-2013. (eDoc no. 00361725)
5. Poisindex Summary Penicillin. Micromedex. 05-Dec-2011. Online access on the 26-12-2012 (eDoc no. 00361756)
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Part II: Module SVII - Identified and potential risks

SVII.1 Newly identified safety concerns (since this module was last submitted)

No new safety concerns have been identified.

SVII.2 Recent study reports with implications for safety concerns

No recent interim or final study reports with implications for safety exist.

SVII.3 Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified)

Identified Risk. Carnitine depletion	
Frequency with 95 % CI	The frequency of carnitine depletion or deficiency as result of treatment with pivmecillinam cannot be estimated from the available study data. Post-marketing seven cases of carnitine decreased and one of carnitine deficiency have been reported for the originator product Selexid®.
Seriousness/outcomes	A cumulative search in the safety database for the originator product Selexid® (until 30-Apr-2013) revealed that seven cases of carnitine decreased have been reported post-marketing. Of these, three were considered serious. In the serious cases all the patients were on long-term treatment with Selexid® and the condition improved after ending treatment. No primary carnitine deficiency was described in these patients. In one non-serious literature case (case no. 105713) the patient was treated with Selexid® 400 mg three times daily for nine days. The patient experienced a striking decrease in total serum carnitine concentration after only one day. No additional adverse events were reported, but serum carnitine was slow to return to normal after cessation of therapy. One case of carnitine deficiency (case no. 105638) has been described post-marketing. This concerned an 82-years-old female treated with Selexid® for 8 months who experienced increasing muscle weakness, malaise, reduced mental function and reduced memory for recent events. At the end of Selexid® treatment she suddenly, after 32 hours of fasting, developed hypotension and nausea. The fasting was stopped by rapid intravenous infusion of 5% glucose and she

	improved within 1-2 hours. Results of further clinical investigation were considered to be characteristic of systemic carnitine deficiency. No genetic analysis was reported. Overall, few cases of carnitine depletion/deficiency have been reported and half of these were considered serious. The outcome of the reported cases have been improved or recovered.
Severity and nature of risk	Carnitine depletion can cause a heterogeneous group of disorders. Muscle metabolism is impaired, causing myopathy, hypoglycaemia, or cardiomyopathy (1). Carnitine depletion may be fatal in children with primary carnitine deficiency if not diagnosed and treated in time (2).
Background incidence/prevalence	Primary carnitine deficiency has a frequency ranging from 1:40,000 to 1:120,000 new-borns in different parts of the world (3-5) and is possibly the second most frequent disorder of fatty acid oxidation after medium chain acyl CoA dehydrogenase deficiency. About 0.5–1% of the population carries one abnormal allele for this condition (3), although the precise frequency of carriers is still unclear. A systematic review suggests that although the incidence of individual diseases may be low, taken collectively the overall incidence of secondary carnitine deficiency may be as high as 1:3000 live births. Included in this group of disorders are the most commonly encountered organic acidurias, including methylmalonic aciduria, propionic acidaemia, isovaleric acidaemia, 3-hydroxy-3-methylglutaric aciduria and glutaric aciduria type 1 (glutaryl CoA dehydrogenase deficiency; GA1) with a collective incidence that may be estimated at around 1:15.000 (6).
Risk groups or risk factors	Primary carnitine deficiency is an autosomal recessive disorder of fatty acid oxidation due to the lack of functional OCTN2 carnitine transporters (2). The lack of the plasma membrane carnitine transporter results in urinary carnitine wasting, low serum carnitine levels (0–5 mM, normal 25–50 mM), and decreased intracellular carnitine accumulation. Patients with primary carnitine deficiency loose most (90–95%) of the filtered carnitine in urine (2). In primary carnitine deficiency the metabolic presentation is more frequent before 2 years of age (2). These patients are more susceptible to increased depletion of the carnitine store. Secondary carnitine deficiency is a secondary biochemical feature of many organic acidemias and fatty acid oxidation defects (6). These patients are more susceptible to increased depletion of the carnitine store.

	Concurrent treatment with valproic acid, valproate or other medication liberating pivalic acid should be avoided due to increased risk of carnitine depletion. Both valproic acid and pivmecillinam may reduce serum carnitine and co-treatment should be avoided as it may lead to depletion of the body carnitine store (7, 8).
Potential mechanisms	Depletion of the body carnitine store may be induced by treatment with pivalic acid containing drugs such as pivampicillin and pivmecillinam (7). Pivalic acid forms an ester with carnitine, pivaloylcarnitine, which is excreted in the urine and free serum carnitine in adults was shown to be reduced to about 50% of the initial values after a few days of treatment. Depletion of the muscle carnitine stores takes considerably longer and it has been estimated to take about 50 days to reduce the muscle carnitine concentration to 50% of the initial value in an adult with treatment with pivalic acid containing drugs (7).
Preventability	As pivmecillinam treatment may lead to depletion of the body carnitine store (7), Pivmecillinam LEO 400 mg film-coated tablets should not be used in patients with genetic metabolic anomalies leading to low carnitine store. 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, it should be stated that concurrent treatment with valproic acid, valproate or other medication liberating pivalic acid should be avoided.
Impact on individual patient	Affected patients can have a predominant metabolic or cardiac presentation. Cardiomyopathy is more frequent in older patients where it may be associated with hypotonia. Children with carnitine deficiency might become lethargic and minimally responsive. If they are not treated promptly with intravenous glucose, they may progress to coma and death (2). Based on this, it is assessed that the impact on the individual patient might be severe and especially in children. However, the condition is rapidly reversed with withdrawal of pivmecillinam and treatment with glucose (2).
Potential public health impact of safety concern	Based on the few cases reported post-marketing for the originator product Selexid® (cumulative search in the safety database until 30-Apr-2013) and the nature of these cases as

	described above, it is assessed that potential public health impact of this safety concern is limited.
Evidence source	The references used are listed in module SVII.6
MedDRA terms	LLTs: Carnitine, Carnitine abnormal, Carnitine decreased, Carnitine deficiency, Serum carnitine decreased and Congenital carnitine deficiency

Potential Risk. Pseudomembranous colitis	
Frequency with 95 % CI	The frequency of pseudomembranous colitis as a result of treatment with pivmecillinam cannot be estimated from the available study data. Post-marketing 7 cases of pseudomembranous colitis and 21 cases of *Clostridium difficile* colitis have been reported for the originator product Selexid®.
Seriousness/outcomes	A cumulative search in the safety database for the originator product Selexid® (until 30-Apr-2013) revealed that 7 events of pseudomembranous colitis have been reported post-marketing. Two of the cases were fatal, while the remaining 5 were non-serious. Four of the non-serious cases reported the outcome recovered/resolved, and one was reported as not recovered/not resolved. The cases all contained very limited information and it was not reported whether the patients received treatment.
Severity and nature of risk	The severity of pseudomembranous colitis may range from mild to possibly fatal (11). Mild cases may manifest as diarrhoea, while severe cases may result in toxic megacolon and colonic perforation (9, 10, 11).
Background incidence/prevalence	*C. difficile* is present in 2-8% of healthy adults and up to 70% of healthy infants (9, 10). Incidence of antibiotic-associated diarrhoea varies from 5-9% depending on the antibiotic type, and pseudomembranous colitis complicates 10% of the cases of antibiotic-associated diarrhoea (11). In 2005 the incidence of *C. difficile* infection in hospitalised patients in the United States was found to be 84:100,000 (10).
Risk groups or risk factors	Pseudomembranous colitis is usually associated with antibiotic use, but also antineoplastic drugs have been associated with the disease (9, 10, 11). High-risk populations include elderly people, patients in intensive care unit or hospital, patients with cancer and those suffering from intestinal ischemia or Hirschsprung disease (10, 11).
Potential mechanisms	Pseudomembranous colitis occurs due to disruption of the

	normal bacterial flora of the colon which results in colonisation with *C. difficile*. The bacteria release both a cytotoxin and an enterotoxin, which cause mucosal inflammation and damage, resulting in diarrhoea and colitis. When adherent yellow or white plaques, pseudomembranes, are present on the intestinal mucosa the disease is called pseudomembranous colitis (10). Clinical symptoms of pseudomembranous colitis may occur on the first day after starting antibiotics or up to 6 weeks later. In most cases, however, symptoms begin 3-9 days after starting the antibiotics (11).
Preventability	As treatment with antibiotics may cause pseudomembranous colitis these should be used prudently (11). Colonisation with *C. difficile* may be prevented by avoiding contamination in e.g. the hospital setting, via good hygiene (11). Treatment of asymptomatic carriers is not recommended, because treatment may prolong carriage, which usually resolves spontaneously (11).
Impact on individual patient	Mild or moderate disease may be treated with antibiotics such as metronidazole or vancomycin (9, 10). Two thirds of patients with toxic megacolon require surgical intervention (11).
Potential public health impact of safety concern	Pseudomembranous colitis may potentially be fatal. However, based on the few cases reported post-marketing for the originator product Selexid® (cumulative search in the safety database until 30-Apr-2013), the potential public health impact of this safety concern is limited, especially when appropriate precautions are taken.
Evidence source	The references used are listed in module SVII.6
MedDRA terms	LLTs: Colitis pseudomembranous, enteritis pseudomembranous, enterocolitis pseudomembranous, pseudomembranous colitis, pseudomembranous enterocolitis, pseudomembranous patch, pseudomembranous proctocolitis.

SVII.4 Identified and potential interactions

SVII.4.1 Overview of potential for interactions

Pivmecillinam is rapidly hydrolysed to the active drug mecillinam, pivalic acid, and formaldehyde after absorption (12). Mecillinam is only metabolised to a limited extent. From 50 to 70% of a parenteral dose may be excreted in the urine within 6 hours by glomerular

filtration and tubular secretion. Some mecillinam is excreted in bile where high concentrations occur (13).

SVII.4.2 Important identified and potential interactions

Interacting substance(s)	Valproate and other medications that liberate pivalic acid (14).
Effect of interaction	Increased risk of carnitine depletion.
Evidence source	Theoretical.
Possible mechanisms	Additive effect due to increased levels of pivalic acid.
Potential health risk	No case reports of this interaction have been seen, the evidence of this interaction is purely theoretical. The health impact of this safety concern is therefore limited.
Discussion	There is a theoretical increased risk of carnitine depletion if pivmecillinam is administered concomitantly with valproate or other medications that liberate pivalic acid. The risk of carnitine depletion associated with use of pivmecillinam is an identified important risk, which is discussed in section SVII.3. There it is stated that the interaction between pivmecillinam and valproic acid or other medications liberating pivalic acid should be included in the Pivmecillinam LEO 400 mg film-coated tablets SmPC.

SVII.5 Pharmacological class effects

SVII.5.1 Pharmacological class risks already included as important identified or potential risks

Not applicable.

SVII.5.2 Important pharmacological class effects not discussed above

Cross-hypersensitivity to penicillins and cephalosporins	
Seriousness/outcomes	Symptoms range from mild to severe and may in the worst case be fatal (15).
Severity and nature of risk	Symptoms include skin rash, serum sickness and anaphylaxis and range from mild to severe (15, 16).

Cross-hypersensitivity to penicillins and cephalosporins	
Frequency with other members of the same or similar pharmacological class with 95 % CI	Not available
Risk groups or risk factors	Risk factors for hypersensitivity to drugs include Epstein-Bar virus infection, chronic lymphatic leukaemia, AIDS/HIV and cystic fibrosis. Patients with asthma have an increased risk of anaphylactic reactions to drugs (15).
Potential mechanisms	Drug hypersensitivity is an immune-mediated reaction to a drug. How primary sensitization occurs and how the immune system is initially involved is unclear, but once a drug stimulates an immune response, cross-reactions with other drugs within and between drug classes can occur, for example to other penicillins if a reaction to one penicillin has occurred (16). Additionally, a patient with known hypersensitivity to cephalosporins have approximately 50% incidence of experiencing an allergic reaction to penicillins (15).
Comment	Drug hypersensitivity to penicillins and cephalosporins should be included as a contraindication in the SmPC.

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Part II: Module SVIII - Summary of the safety concerns

Table 3 Summary of safety concerns	
Summary of safety concerns	
Important identified risks	Carnitine depletion
	Cross-hypersensitivity to penicillins and cephalosporins
Important potential risks	Pseudomembranous colitis
Important missing information	Not applicable

Part III: Pharmacovigilance Plan

III.1 Safety concerns and overview of planned pharmacovigilance actions

Carnitine depletion		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Only routine pharmacovigilance activities are planned	None

Cross-hypersensitivity to penicillins and cephalosporins		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Only routine pharmacovigilance activities are planned	None

Pseudomembranous colitis		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Only routine pharmacovigilance activities are planned	None

III.2 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

Not applicable.

III.3 Studies and other activities completed since last update of Pharmacovigilance Plan

Not applicable.

III.4 Details of outstanding additional pharmacovigilance activities

III.4.1 Imposed mandatory additional pharmacovigilance activity (key to benefit risk)

Not applicable.

III.4.2 Mandatory additional PhV Activity (being a Specific Obligation)

Not applicable.

III.4.3 Required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimisation measures

Not applicable.

III.4.4 Stated additional pharmacovigilance activities

Not applicable.

III.5 Summary of the Pharmacovigilance Plan

III.5.1 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Not applicable.

III.5.2 Table of completed studies/activities from the Pharmacovigilance Plan

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

IV.1 Applicability of efficacy to all patients in the target population

The originator product Selexid® is a well-established product which has been on the market for more than 35 years. Clinical trials evaluating pivmecillinam and mecillinam for treatment of acute uncomplicated urinary tract infection have been published over several decades. The early trials, while appropriate for their time, would now be considered to be limited by some aspects of the study design. Most of these were open label and enrolled small study subject numbers. However, clinical trials have consistently documented the efficacy of mecillinam and pivmecillinam for treatment of acute uncomplicated urinary tract infection. The clinical efficacy has varied from 85 – 100% and the microbiological efficacy from 75 – 100%. In comparative trials, pivmecillinam is usually equivalent to comparators; the efficacy rates reported are similar to those reported for fosfomycin and nitrofurantoin (1, 2), which are recommended for empiric therapy for acute uncomplicated urinary tract infection. While one study reported clinical outcomes with 3 days of therapy were significantly better with norfloxacin compared to pivmecillinam, the clinical outcomes for women under 50 years of age were similar (3).

Studies consistently report little impact of pivmecillinam on the normal gut or vaginal flora of young women, and no impact on anaerobic organisms (4, 5). Treatment with pivmecillinam does not lead to cross resistance with any other antimicrobial agents. Thus, pivmecillinam and mecillinam is uniquely suited for the treatment of acute uncomplicated urinary tract infection given current concerns about increasing resistance to important antimicrobial agents against *E. coli* and other bacterial strains (1, 6). Resistance to pivmecillinam in community *E. coli* has not developed in countries where there has been prolonged, substantial use (6).

Pivmecillinam is recommended as first choice for empiric treatment of acute uncomplicated urinary tract infection in the International Guidelines of the IDSA and European CMID (1), as well as in the European Urology Guidelines (7). Further, mecillinam is considered an appropriate antimicrobial for empirical therapy of uncomplicated cystitis in most regions (1). There has been substantial use of this antibiotic for decades in some countries where it is licensed for the treatment of acute uncomplicated urinary tract infection. Thus, there is substantial evidence and experience to support use of pivmecillinam antimicrobial for empiric treatment of acute, uncomplicated cystitis.

Pro-drugs such as pivampicillin, bacampicillin, pivmecillinam and cefuroxime axetil are also favourable from an ecological point of view as they are not active against the bacteria in the mouth and the intestine (before absorption) and are not excreted to a significant degree via the intestine, saliva or skin. Mecillinam (the active form of the drug) is also biodegradable and thus environmentally responsible (8). These properties lead to a decreased potential for development of resistance, an important issue with regard to the increasing global concerns over emerging bacterial resistance (6). Experience from Scandinavia supports this, since resistance to mecillinam after 20 years of use is low (about 5%) and stable (9).

IV.2 Tables of post-authorisation efficacy studies

No post-authorisation efficacy studies are planned.

IV.3 Summary of Post authorisation efficacy development plan

Not applicable.

IV.4 Summary of completed Post authorisation efficacy studies

Not applicable.

IV.5 Reference list

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Part V: Risk minimisation measures

V.1 Risk minimisation measures by safety concern

Safety concern	**Carnitine depletion**
Objective(s) of the risk minimisation measures	To minimise the number of events of carnitine depletion associated with use of Pivmecillinam LEO 400 mg film-coated tablets.
Routine risk minimisation measures	Inclusion of the risk in the SmPC: 4.3 Contraindication Statement that use of pivmecillinam LEO 400 mg film-coated tablets is contraindicated in patients with genetic metabolism anomalies known to be leading to severe carnitine deficiency such as carnitine transporter defect, methylmalonic aciduria or propionic acidaemia. 4.4 Special warnings and special precautions for use A warning that long-term use increases the risk of carnitine deficiency. 4.5 Interaction with other medicinal products and other forms of interaction Statement that concurrent treatment with valproic acid, valproate or other medication liberating pivalic acid should be avoided due to increased risk of carnitine depletion.
Additional risk minimisation measure(s)	Not applicable.

Safety concern	**Cross-hypersensitivity to penicillins and cephalosporins**
Objective(s) of the risk minimisation measures	To avoid incidences of hypersensitivity to mecillinam in patients with cross-hypersensitivity.
Routine risk minimisation measures	Inclusion of the risk as a contraindication in the SmPC: 4.3 Contraindication Inclusion of hypersensitivity to penicillins and cephalosporins as a contraindication.
Additional risk minimisation measure(s)	Not applicable.

Safety concern	**Pseudomembranous colitis**
Objective(s) of the risk minimisation measures	To minimise the number of events of pseudomembranous colitis associated with use of Pivmecillinam LEO 400 mg film-coated tablets.
Routine risk minimisation measures	Inclusion of the risk in the SmPC: 4.4 Special warnings and special precautions for use 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.
Additional risk minimisation measure(s)	Not applicable.

Effectiveness of risk minimisation measures for carnitine depletion	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of the risk minimisation measures will be based on the number of cases reporting carnitine depletion
Criteria for judging the success of the proposed risk minimisation measures	No increase in frequency of case reports reporting relevant adverse reactions.
Planned dates for assessment	Half-yearly as part of signal detection
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	-

Effectiveness of risk minimisation measures for cross-hypersensitivity to penicillins and cephalosporins	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of the risk minimisation measures will be based on the number of cases reporting cross-hypersensitivity
Criteria for judging the success of the proposed risk minimisation measures	No increase in frequency of case reports reporting relevant adverse reactions.
Planned dates for assessment	Half-yearly as part of signal detection
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	-

Effectiveness of risk minimisation measures for pseudomembranous colitis	
How effectiveness of risk minimisation measures for the safety concern will be measured	The effectiveness of the risk minimisation measures will be based on the number of cases reporting pseudomembranous colitis
Criteria for judging the success of the proposed risk minimisation measures	No increase in frequency of case reports reporting relevant adverse reactions.
Planned dates for assessment	Half-yearly as part of signal detection
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	-

V.2 Risk minimisation measure failure (if applicable)

Not applicable.

V.3 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Carnitine depletion	Inclusion of contraindication and warning in the SmPC (section 4.3, 4.4 and 4.5) and PIL	Not applicable
Cross-hypersensitivity to penicillins and cephalosporins	Inclusion of contraindication in the SmPC (section 4.3) and PIL	Not applicable
Pseudomembranous colitis	Inclusion of warning in the SmPC (section 4.4) and PIL	Not applicable

Part VI: Summary of activities in the risk management plan

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	Carnitine depletion
	Cross-hypersensitivity with penicillins and cephalosporins
Important potential risks	Pseudomembranous colitis
Important missing information	Not applicable

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Not applicable

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Carnitine depletion	Inclusion of contraindication and warning in the SmPC (section 4.3, 4.4 and 4.5) and PIL.	Not applicable
Cross-hypersensitivity to penicillins and cephalosporins	Inclusion of contraindication in the SmPC (section 4.3) and PIL.	Not applicable
Pseudomembranous colitis	Inclusion of warning in the SmPC (section 4.4) and PIL	Not applicable

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.

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Available in electronic format only.

Annex 2 – SmPC & Package Leaflet

DCP SmPCs

Proposed SmPC DCP Pivmecillinam LEO 400 mg film-coated tablets (eDoc no. 00360040)

Package leaflet

Package leaflets are available on request.

Annex 3 – Worldwide marketing authorization by country (including EEA)

Not applicable.

Annex 4 - Synopsis of on-going and completed clinical trial programme

Not applicable.

Annex 5 - Synopsis of on-going and completed pharmacoepidemiological study programme

Not applicable.

Annex 6 - Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III

Not applicable.

Annex 7 - Specific adverse event follow-up forms

Not applicable.

Annex 8 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 9 - Newly available study reports for RMP parts III & IV

Not applicable.

Annex 10 - Details of proposed additional risk minimisation measures (if applicable)

Not applicable.

Annex 11 - Mock-up of proposed additional risk minimisation measures (if applicable)

Not applicable.

Annex 12 - Other supporting data (including referenced material)

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