HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

3 April 2013

SELEXID 200 mg, film-coated tablet

B/12 (CIP: 34009 379 930 5 0)

Applicant: LEO PHARMA

INN	Pivmecillinam (hydrochloride)
ATC Code (2012)	J01CA08 **(**antibiotic related to the beta-lactam family**)**
Reason for the request	**Inclusion**
List(s) concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication(s) concerned	**"They are derived from the antibacterial activity and pharmacokinetic characteristics of SELEXID. They take account both of the clinical studies to which this medicine has given rise and of its place in the range of antibacterial products currently available.** **They are limited to urinary tract infections due to the organisms defined above as sensitive.** **The official guidelines on the appropriate use of antibacterials must be taken into consideration."**

Actual benefit	**<u>Substantial</u> only in the case of acute uncomplicated cystitis in women.** **<u>Insufficient</u> for reimbursement for hospital use in view of the treatment alternatives available for other urinary tract infections: acute complicated cystitis, pyelonephritis and acute prostatitis.**
Improvement in Actual Benefit	**Given the absence of any comparative studies versus the alternatives currently used in France in the treatment of acute uncomplicated cystitis in women, the Committee considers that the proprietary medicinal product SELEXID does not provide any improvement in actual benefit (IAB V, nonexistent) in the management of acute uncomplicated cystitis in women.**
Therapeutic use	**Pivmecillinam is a possible option in cases of acute uncomplicated cystitis in women, in view of:** **- its proven efficacy in this clinical setting, with a satisfactory safety profile,** **- its activity on most enterobacteriaceae, including on certain strains producing extended-spectrum beta-lactamases (ESBL),** **- the lack of cross-resistance to other beta-lactams,** **- the ability to use it during pregnancy,** **- the interest in limiting the use of fluoroquinolones and sulfonamides because of the risk of resistance development.** **However, reduced efficacy, particularly microbiological, has been described when it is used in a short treatment for 3 days. In addition, uncertainties remain about the optimal dosage and duration (from 6 to 8 days in most cases but possibly from 3 to 4 days in common, uncomplicated conditions) of treatment with this antibiotic, and about the current level of *E. coli* resistance to pivmecillinam in France.** **Pivmecillinam has no place in therapeutic use to treat acute complicated cystitis, pyelonephritis or acute prostatitis, given the absence of any proof of efficacy in these types of infections.**
Recommendations	**Given the broad indication of the Marketing Authorisation for this antibiotic (*"urinary tract infections with organisms sensitive to pivmecillinam"* with no distinction between upper or lower, uncomplicated or complicated), the Committee recommends revision of the Marketing Authorisation for pivmecillinam so as to better target the population likely to benefit from this antibiotic and to clarify the duration of use and dosage which vary greatly between the studies. The Committee will consider revising its opinion according to the conclusions reached.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date initiated: 10/04/1981 (national procedure);
Prescribing and dispensing conditions / special status	List I

ATC Classification	2012	
	J	Antiinfectives for systemic use
	J01	Antibacterials for systemic use
	J01C	Beta-lactam antibacterials: penicillins
	J01CA	Penicillins with extended spectrum
	J01CA08	Pivmecillinam

02 BACKGROUND

This is an application for inclusion on the list of proprietary medicinal products reimbursed by National Insurance and on the list of medicines approved for hospital use.

This medicine was included on the list of medicines approved for hospital use and reimbursed by National Insurance in 1984 until it was excluded from reimbursement in 2002, at the request of the company.
In the previous assessment (reassessment of the AB in January 2001), the Transparency Committee assigned to SELEXID 200 mg a substantial AB in the indications of the Marketing Authorisation, but an efficacy/adverse effects ratio that was rated as moderate.

The AFSSAPS guidelines of 2008[1] on the management of community-acquired urinary tract infections in adults position pivmecillinam (SELEXID) solely in the following situations, on microbiological documentation:

- *"complicated cystitis (excluding, with some exceptions, infections in men which must be treated as prostatitis), after an antibiotic sensitivity test where treatment lasts at least 5 days,*
- *gestational bacteriuria and acute cystitis, after an antibiotic sensitivity test where treatment lasts at least 5 days.*

The high incidence of acquired resistance means that it cannot be used in France for the empirical treatment of acute cystitis.
Pivmecillinam is not recommended in the treatment of community-acquired urinary tract infections with parenchymal involvement (pyelonephritis, prostatitis)."

03 THERAPEUTIC INDICATIONS

"They are derived from the antibacterial activity and pharmacokinetic characteristics of SELEXID. They take account both of the clinical studies to which this medicine has given rise and of its place in the range of antibacterial products currently available.

They are limited to urinary tract infections due to the organisms defined above as sensitive.

[1] AFSSAPS: Good practice guidelines. Diagnosis and antibiotic therapy of community-acquired bacterial urinary tract infections in adults. June 2008. Available on the SPILF website: http://www.infectiologie.com/site/consensus_recos.php

The official guidelines on the appropriate use of antibacterials must be taken into consideration."

04 DOSAGE

"Patients with normal renal function:
Average dosage:
600-800 mg in 2 or 3 doses in the morning (midday) and the evening (i.e. about 10-13 mg/kg/day), which can be increased to 1200-1600 mg in 2 or 3 doses, in the morning (midday) and the evening if necessary.
In all cases, it seems unnecessary to exceed 1600 mg/day.
Duration of treatment:
6-8 days in most cases, depending on the severity of the symptoms. In common uncomplicated conditions, treatment for 6 days is generally sufficient and in some cases can possibly be for 3-4 days.

In patients with renal impairment:
The loading dose will be identical: the maintenance dose will then be reduced in line with the reduction in the creatinine clearance. When glomerular filtration is between 15 and 30 ml/min, divide the dosage by two. When glomerular filtration is below 15 ml/min, divide the dosage by three."

05 THERAPEUTIC NEED[1,2]

Urinary tract infections (UTIs) are very common diseases with an overall incidence of 4-6 million cases a year,[3] constituting the second commonest site of bacterial infection after the respiratory system. The incidence is higher in women than in men.
These infections correspond to different settings combining clinical signs, local or general, and laboratory signs. They are most often harmless, but can be serious if there is parenchymal involvement (pyelonephritis, prostatitis) or if they occur in a particular setting (materno-fetal repercussions of a gestational infection).
Clinically, a distinction must be made between:

- "simple" UTIs, also called uncomplicated UTIs. In practice, they affect only women with no other particular susceptibility;
- "complicated" UTIs, for which there is not necessarily a constitutional complication but at least a risk factor for complications which can make the infection more severe and the treatment more complex;
- irrespective of whether they are initially simple or complicated, the UTI may, if located in the parenchyma, be accompanied by severe sepsis and be life-threatening.

The risk factors for complications are:

- an organic or functional disease of the urinary system (residual urine in the bladder, reflux, lithiasis, tumour, recent urological procedure, etc.)
- a special pathological situation (diabetes, immunosuppression, renal impairment, etc.),
- particular physiopathological susceptibility (elderly patient with a comorbidity, pregnancy, man). Urinary tract infections in men are by definition complicated and any cystitis in men must, except in exceptional cases, be regarded and treated as acute prostatitis.

Urinary tract colonisation, or asymptomatic bacteriuria to use the traditional term, is a situation in which microorganisms are present in the urine, without themselves giving rise to clinical signs.

Urinary tract infections in adults outside pregnancy include: uncomplicated urinary colonisation (no antibiotic treatment), acute uncomplicated cystitis, acute complicated cystitis, acute recurring cystitis, acute uncomplicated pyelonephritis, acute complicated pyelonephritis, acute prostatitis.

[2] CMIT. Urinary tract infections: In E. PILLY: Vivactis Plus Ed; 2012: pp 217-220
[3] Elkharrat D, Arrouy L, Benhamou F, Dray A, Grenet J, Le Corre A. Epidemiology of community-acquired urinary tract infections in adults in France. Springer 2007; pp 1-20.

During pregnancy, three clinical conditions can be described: asymptomatic bacteriuria, acute gestational cystitis and acute gestational pyelonephritis.

Bacteriologically, urinary tract infections are marked by:

- great stability of the species involved, with *Escherichia coli* in 1st place (60-80% of all clinical forms together; 70-95% of acute uncomplicated cystitis; 85-90% acute uncomplicated pyelonephritis) in front of either *Staphylococcus saprophyticus* (5-10% of cases of uncomplicated cystitis), or *Proteus* (5-10% of other forms) then other, rarer species (*Klebsiella, Enterobacter, Serratia, enterococci*).
- growing and worrying antibiotic resistance, with *E. coli* reaching 40-50% for amoxicillin, 25-30% for the combination amoxicillin-clavulanic acid, 25% for pivmecillinam, 20-40% for co-trimoxazole, about 15% for first-generation quinolones and 10% for fluoroquinolones, less than 5% for 3rd-generation cephalosporins, aminoglycosides, furans and fosfomycin trometamol. The risk of antibiotic resistance is increased in the event of recent antibiotic therapy, for whatever reason, and particularly where a fluoroquinolone was taken within 6 months.

The recommended antibiotic therapy for different clinical situations is shown in Table 1 (summary based on AFSSAPS recommendations of 2008). The place of each antibiotic is based not only on efficacy and toxicity criteria but also on an analysis of the ecological risk, so as to limit the emergence of bacterial resistance.

Table 1 Antibiotic therapy during urinary tract infections in adults

Urinary tract infections in adults: Antibiotic therapy		
Uncomplicated or recurring cystitis, outside pregnancy: empirical treatment		
Empirical, 1st line	Fosfomycin trometamol ***Fosfomycin trometamol is favoured as 1st line treatment so as to save the fluoroquinolone class and because of its simplicity of use.***	3 g PO single dose (monodose treatment)
Empirical, 2nd line	Nitrofurantoin**	100 mg x 3/day PO, for 5 days
	Fluoroquinolones (PO, in a single dose or as a 3-day treatment)	
	Ciprofloxacin	500 mg single dose or 250 mg x 2/day, for 3 days
	Lomefloxacin	400 mg x 1/day, for 3 days
	Norfloxacin	400 mg x 2/day, for 3 days
	Ofloxacin	400 mg single dose or 200 mg x 2/day, for 3 days
In view of the acquired resistance, the following substances can no longer be recommended in empirical treatment: beta-lactams and related substances (amoxicillin, co-amoxiclav, 1st and 2nd generation cephalosporin, pivmecillinam) and co-trimoxazole (sulfamethoxazole-trimethoprim).		
Antibiotic prophylaxis in cases of recurring cystitis: To be analysed case by case		
Complicated cystitis, outside pregnancy: avoid empirical treatment if possible and make the appropriate choice at the outset		
Empirical, 1st line	Nitrofurantoin**	100 mg x 3/day PO, duration ≥ 7 days
Empirical, 2nd line	Cefixime	200 mg x 2/day PO, duration ≥ 5 days
	Fluoroquinolones (PO, duration ≥ 5 days)	
	Ciprofloxacin	500 mg to 750 mg x 2/day
	Ofloxacin	200 mg x 2 to 3/day
	Enoxacin	200 mg × 2/day
	Lomefloxacin	400 mg × 1/day
	Norfloxacin	400 mg × 2/day
Others selected according to antibiotic sensitivity test	Amoxicillin or co-amoxiclav	1g PO x 3/day, duration ≥ 5 days
	Pivmecillinam	400 mg PO x 2/day, duration ≥ 5 days
	Co-trimoxazole	"high" dose: 1 tablet PO x 2/day, duration ≥ 5 days
Gestational cystitis and asymptomatic bacteriuria in pregnant women*		
Asymptomatic bacteriuria: treatment after obtaining the results of an antibiotic sensitivity test	Amoxicillin or co-amoxiclav*	1g PO x 3/day, duration ≥ 5 days
	Cefixime	200 mg PO x 2/day, duration ≥ 5 days
	Pivmecillinam	400 mg PO x 2/day, duration ≥ 5 days
	Nitrofurantoin**	100 mg PO x 3/day, duration ≥ 7 days
	Co-trimoxazole*	"high" dose: 1 tablet PO x 2/day, duration 5 days
Gestational cystitis	***Empirical treatment***	
	Cefixime	200 mg PO x 2/day, duration ≥ 5 days
	Nitrofurantoin**	100 mg PO x 3/day, duration ≥ 7 days
	Other possible treatments after obtaining the results of an antibiotic sensitivity test	
	Amoxicillin	1g PO x 3/day, duration ≥ 5 days

	or co-amoxiclav*	
	Pivmecillinam	400 mg PO x 2/day, duration ≥ 5 days
	Co-trimoxazole*	"high" dose: 1 tablet PO x 2/day, ≥ 5 days
Acute uncomplicated/complicated, gestational pyelonephritis, acute prostatitis. Duration of treatment: 10-14 days or even 21 according to clinical symptoms; if fluoroquinolones 7 days in cases of uncomplicated pyelonephritis.		
Beta-lactams: injectable 3rd generation cephalosporins	Ceftriaxone (IM/IV) Cefotaxime (IM/IV/SC)	1 g x 1/day or even 2 g x 1/day 1 g x 3/day or even 2 g x 3/day
Fluoroquinolones: PO or injectable if oral route impossible (**if pregnancy: expert opinion**)	Ciprofloxacin Levofloxacin Ofloxacin	500-750 mg PO x 2/day, if IV 400 mg x 2-3/day 500 mg x 1/day PO or IV 200 mg x 2-3/day PO or IV
Monobactams (if allergy or intolerance to other substances)	Aztreonam (IV/IM)	1 g x 2/day, or even 1 g x 3/day
Aminoglycosides (IV or IM): 1-3 days in dual therapy if severe form (**if pregnancy: expert opinion**)	Gentamicin Netilmicin Tobramycin	3 mg/kg x 1/day 6 mg/kg × 1/day 3 mg/kg × 1/day
Follow-on oral treatment after obtaining the results of an antibiotic sensitivity test	Amoxicillin or co-amoxiclav* Cefixime Co-trimoxazole*	1 g PO x 3/day 200 mg PO x 2/day "high" dose: 1 tablet PO x 2/day

* **Pregnancy: Co-amoxiclav** (to be avoided if birth imminent), **co-trimoxazole** (to be avoided as a precaution in the first trimester).

****Nitrofurantoin: the hepatic and pulmonary toxicity of nitrofurantoin, particularly in prolonged treatments, especially for the prophylaxis of recurring urinary infections, led AFSSAPS to make a reassessment, in 2011, of the indications and conditions for the prescription and use of this antibiotic (cf. letter to healthcare professionals).**

Letter to healthcare professionals (March 2012): "*AFSSAPS, after reassessing the risk/benefit ratio of nitrofurantoin-based proprietary medicinal products (FURADANTINE®, capsule; FURADOINE®, tablet - Merck Serono - and MICRODOÏNE®, capsule – Du Goménol), wishes to inform healthcare professionals of important changes to the conditions for use of these medicines: from now on, in the curative treatment of cystitis, the prescription of nitrofurantoin-based proprietary medicinal products must be restricted to girls from 6 years of age, adolescent girls and adult women when: - the cystitis is demonstrably due to sensitive organisms; - and when another antibiotic with a better risk/benefit ratio cannot be used orally. Their use can nevertheless be considered in empirical treatment if the patient's condition necessitates the initiation of emergency treatment and/or on the basis of the patient's medical history (in cases of recurring cystitis due to multiresistant bacteria). On the other hand, these proprietary medicinal products must no longer be used in the prophylactic treatment of recurring urinary tract infections (continuous or intermittent treatments). In addition, because of the potential serious immunoallergic risk, repeated treatments must be avoided."*

Resistance development and therapeutic considerations (according to HCSP 2010)[4]

Escherichia coli is the leading cause of urinary tract infections and has progressively become the bacterial species most affected by the emergence of **extended-spectrum beta-lactamases (ESBLs)**, enzymes which inactivate most beta-lactams except for cephamycins and carbapenems. These multiresistant enterobacteriaceae are subject to special monitoring in France.

According to the HCSP, the guidelines (AFSSAPS 2008) on the first-line treatment of urinary tract infections are not being called into question at present, but will need to be reconsidered in the light of changes in the percentage of *E. coli ESBLs* identified among the *E. coli* infections observed in the community. It is necessary to favour, as far as possible, the use of documented antibiotic therapies and to limit the use made of empirical antibiotic therapies. Thus, as regards the management of complicated cystitis, but in the absence of any sign of severity, it is possible to consider delaying the initiation of antibiotic therapy until an antibiotic sensitivity test has been performed.

As regards pyelonephritis and prostatitis, the reference empirical treatment today is a 3rd generation (parenteral) cephalosporin or a fluoroquinolone (oral or parenteral, in adults only). The guidelines make provision for the addition of an aminoglycoside for the more severe forms of community-acquired urinary tract infections (severe sepsis, obstructive pyelonephritis, neonates

[4] High Council for Public Health (HCSP). Guidelines on the measures to be taken to prevent the emergence of ESBL enterobacteriaceae to combat their spread; proposals drafted with a view to defining a national programme of prevention. February 2010.

and babies under 3 months of age, etc.); this addition partly covers the risk of failure in cases of *E. coli* ESBLs, since French strains are still sensitive to aminoglycosides in about 50% of cases.

Faced with a documented or strongly suspected infection with an *E. coli* ESBL:
(a) it will be necessary to favour substances other than carbapenems;
(b) since the use of carbapenems is restricted to the management of severe infections: imipenem, meropenem or doripenem (only in cases of complicated urinary tract infections), ertapenem (marketing authorisation in intra-abdominal infections) possibly combined with aminoglycosides. It must be borne in mind that the use of carbapenems is a bogus good solution – a solution which is effective in terms of the individual therapy but one which has a high risk of promoting the development of carbapenemases (a risk which applies on both individual and collective levels).
Finally, the development of resistance to fosfomycin, but also to furans, will have to be monitored particularly carefully, because their use opens the way to the appearance of resistance; thus, resistance to fosfomycin, which is currently still less than 2% in France, reaches 25% according to some Spanish data – the development of this resistance seems to be correlated with the increase in use of this substance.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The clinically relevant comparators are antibiotics for oral use, which are recommended in the treatment of community-acquired urinary tract infections:

Antibiotic (nonproprietary name)	Trade name of the originator medicinal product (company)
Beta-lactams, penicillin	
Amoxicillin	Several presentations
Aminopenicillin + beta-lactamase inhibitor	
Amoxicillin + clavulanic acid	AUGMENTIN (GLAXOSMITHKLINE), CIBLOR (Pierre FABRE MEDICAMENT)
Third-generation cephalosporin	
Cefixime	OROKEN (SANOFI AVENTIS)
Phosphonic acid derivative	
Fosfomycin trometamol	MONURIL (ZAMBON), URIDOZ (LUCIEN THERABEL PHARMA)
Nitrofurans	
Nitrofurantoin	FURADANTINE, FURADOINE (MERCK LIPHA SANTE FRANCE), MICRODOINE (DU GOMENOL)
Fluoroquinolones	
Ciprofloxacin	CIFLOX (BAYER)
Ofloxacin	OFLOCET (SANOFI AVENTIS)
Enoxacin	ENOXOR (PIERRE FABRE)
Lomefloxacin	LOGIFLOX, DECALOGIFLOX (BIOCODEX)
Norfloxacin	NOROXINE (MSD – CHIBRET)
Sulfonamide + trimethoprim	
Sulfamethoxazole-trimethoprim	BACTRIM (ROCHE)

For information, the following antibiotics (parenteral forms) are recommended in the treatment of community-acquired urinary tract infections with parenchymal involvement (pyelonephritis or prostatitis):

- Injectable 3rd generation cephalosporins: cefotaxime, ceftriaxone
- Monobactams: aztreonam
- Aminoglycosides: gentamicin, netilmicin, tobramycin

◗ Conclusion

The clinically relevant comparators are antibiotics for oral use which are recommended in the treatment of community-acquired urinary tract infections.

06.2 Other health technologies

Not applicable

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

For Europe, SELEXID 200 mg, tablet (box of 12) is marketed in Austria.

Other presentations, dosages and other packagings are available.

Proprietary medicinal product	Dosage	Packaging	Marketed in
SELEXID	**200 mg**	Box of 10	United Kingdom
		Box of 12	Austria
		Box of 12	Morocco
		Box of 12	Tunisia
		Box of 14	Finland
		Box of 14	Portugal
		Box of 14	Sweden
		Box of 15	Norway
		Box of 20	Denmark
		Box of 20	Iceland
		Box of 24	Greece
SELEXID	**400 mg**	Box of 10	Denmark
		Box of 10	Norway
		Box of 10	Sweden
		Box of 20	Iceland

08 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion (reason for review)	10 January 2001 (reassessment of AB)
Indication	Treatment of urinary tract infections due to organisms defined in Pharmacodynamics as sensitive.
AB (wording)	*Substantial* AB Efficacy/adverse effects ratio *moderate*
IAB (wording)	Not applicable
Studies requested	Not applicable

09 ANALYSIS OF AVAILABLE DATA

The company submitted two published clinical studies:

- a study[5] comparing the efficacy of pivmecillinam (400 mg x 3/day, for 3 days) with that of sulfamethizole (1g x 2/day, for 3 days), in the treatment of uncomplicated acute cystitis in women aged 18 to 65 years. It should be noted that the comparator chosen in this study is not recommended in France in the treatment of urinary tract infections and the dose evaluated (1 g x 2/day, for 3 days) does not correspond to the dosage recommended in its French Marketing Authorisation (200 mg x 3/day, for 3-4 days). This study was performed in Denmark between January 2003 and December 2004 (inclusion period).
- a controlled study[6] versus placebo, evaluating different dosages and periods of use of pivmecillinam (200 mg x 3/day for 7 days, 200 mg x 2/day for 7 days and 400 mg x 2/day for 3 days) in the treatment of acute uncomplicated cystitis. This study was performed in Sweden between April 1995 and December 1997 (inclusion period).
- summary of the safety data.

No comparative study versus the antibiotics currently recommended in France in the management of urinary tract infections was submitted by the company.

09.1 Efficacy

➢ ***Acute uncomplicated cystitis***

Study by Bjerrum L. et al (2009): Pivmecillinam versus sulfamethizole, in 3 days' treatment

In this double-blind, randomised, controlled clinical study, the efficacy of pivmecillinam (400 mg x 3/day, for 3 days) was compared with that of sulfamethizole (1 g x 2/day, for 3 days), in the treatment of acute uncomplicated cystitis in women aged 18 to 65 years (n = 175 randomised patients), with no episode of urinary infection in the 3 months before inclusion, with no antibacterial treatment during the preceding 2 weeks.

The primary efficacy endpoint was clinical cure, defined as a "reduction in urinary symptoms such as dysuria or pollakiuria and the disappearance of these symptoms at the follow-up visits between the 7th and the 10th day (D7 to D10) after the start of treatment."

Among the 175 randomised patients, 167 were included in the analysis of cure (86 in the pivmecillinam group and 81 in the sulfamethizole group) and 123 in the bacteriological analysis. *E. coli* was the pathogen most commonly isolated (> 80% of positive cultures).

At the follow-up visit (D7 to D10), no difference was observed between the two treatments in terms of clinical cure (95.2% in the pivmecillinam group versus 92.6% in the sulfamethizole group; difference 2.8% [95% CI: -4.5; 10.0]) and bacteriological cure (68.8% versus 77.9%; difference -9.2% [-24.7%; 6.3%]).

However, the results of this study must be interpreted with care because of the small size of the populations included (it was planned to include 320 patients in the study, 160 in each group).

Study by Ferry S.A. et al. (2007): Treatment with pivmecillinam for 3 days or 7 days versus placebo

This double-blind, randomised, controlled clinical study compared the efficacy of treatment with **pivmecillinam for 3 days** (in a dosage of 400 mg x 2/day) or **for 7 days** (in a dosage of 200 mg x 3/day or 200 mg x 2/day) versus placebo, in women aged 18 years and over, with a diagnosis of acute uncomplicated cystitis (n = 1143 randomised patients), with no antibacterial treatment during the preceding month.

[5] Bjerrum L. et al. Pivmecillinam versus sulfamethizole for short-term treatment of uncomplicated acute cystitis in general practice: a randomized controlled trial. Scandinavian Journal of Primary Health Care. 2009; 27: 6-11.

[6] Ferry S.A. et al. Clinical and bacterial outcome of different doses and duration of pivmecillinam compared with placebo therapy of uncomplicated lower urinary tract infection in women: the LUTIW project. Scandinavian Journal of Primary Health Care. 2007; 25: 49-57.

The primary efficacy endpoint was clinical cure, defined as the "disappearance of urinary symptoms during and after treatment" and bacteriological cure, defined as the "eradication of bacteriuria at the 2 follow-up visits (between 8-10 days and 35-49 days after the start of treatment)."

Among the 1143 randomised patients, 884 (77%) with significant bacteriuria were followed up and included in the analysis of cure (217 in the pivmecillinam group 200 mg x 3 x 7 days, 220 in the group 200 mg x 2 x 7 days, 220 in the group 400 mg x 2 x 3 days versus 227 in the placebo group). *E. coli* was the pathogen most commonly isolated (62.1% of positive cultures).

At the 2 follow-up visits (between 8-10 days and 35-49 days), the 3 pivmecillinam protocols were superior to placebo, with percentages of clinical and bacteriological cure (combined analysis) varying between 56 and 58% in the pivmecillinam groups versus 21% in the placebo group ($p < 0.001$). The 7-day pivmecillinam protocols were superior to the 3-day protocol as regards bacteriological cure between the 8th and the 10th day (93-94% in the 7-day protocols versus 84% in the 3-day protocol). The authors recommend using pivmecillinam (200 mg x 2/day) in 7 days' treatment.

Other clinical studies (data taken into account in the AFSSAPS guidelines of 2008)
The results of the study by Ferry SA et al. described above confirm those of two older studies. In fact:

- in a double-blind, randomised controlled clinical study[7] performed in 955 patients with a diagnosis of acute cystitis for less than 7 days, pivmecillinam (400 mg x 2/day) in 3 days' treatment was inferior to norfloxacin (400 mg x 2/day), with a percentage of bacteriological eradication of 75% of patients treated with pivmecillinam versus 91% of patients treated with norfloxacin ($p < 0.001$); on the other hand, no significant difference was found between the two substances with a treatment duration of 7 days for pivmecillinam;
- in another study,[8] pivmecillinam (400 mg x 2/day) for 3 days was compared with the substance taken for 7 days in a dosage of 200 mg 2 times a day. Bacteriological eradication was 79% in patients treated for 3 days versus 90% in 7 days' treatment ($p = 0.002$). Consequently, the authors recommend using pivmecillinam (200 mg x 2/day) in 7 days' treatment.

- ***Acute complicated cystitis, pyelonephritis and prostatitis.***

No clinical study was submitted in these clinical situations.

09.2 Adverse effects

Clinical studies (Bjerrum L. et al. 2009; Ferry SA. et al. 2007)
In these two studies, adverse effects (AE) were uncommon (14.1% in the pivmecillinam group versus 12.8% in the sulfamethizole group in one study; and 12-17% in the pivmecillinam groups versus 12% in the placebo group in the other study); the commonest adverse effects were digestive disorders (nausea and diarrhoea).

Pharmacovigilance data
Pivmecillinam is marketed internationally in the form of tablets and vials of powder for solution for injection (IV/IM).
The company submitted a pharmacovigilance summary with data from the PSURs covering the period from 1 June 2003 to 31 August 2010. The number of treatments sold in this period is estimated to be 11,093,000 for both forms combined.

[7] Nicole LE. Pivmecillinam in the treatment of urinary tract infection. J Antimicrob Chemother. 2000;46 Suppl 1:35-9; discussion 63-5
[8] Nicolle LE, Madsen KS, Debeek GO et al. Three days of pivmecillinam or norfloxacin for treatment of acute uncomplicated urinary infection in women. Scand J Infect Dis. 2002;34:487-492

The adverse effects reported (159 in total) during this period did not give rise to any particular pharmacovigilance alerts. The main adverse effects reported were, according to the MedDRA classification:

- "Gastrointestinal disorders" (33/159), including diarrhoea (4 cases), vomiting (8) and nausea (7),
- "Skin and subcutaneous tissue disorders" (32/159), including urticaria (6), generalised pruritus (4) and rash (4),
- "General disorders and administration site conditions" (15/159),
- "Investigations" (14/159),
- "Nervous system disorders" (12/159).

Cumulative international experience has identified a group of events of the peripheral neuropathy type, with symptoms such as paraesthesia and motor disorders. This type of effect is being monitored to check whether or not it constitutes a possible new signal for pivmecillinam.

Adverse effects according to the SPC

- **"Rare:**
  - Gastrointestinal disorders: nausea, vomiting, diarrhoea, candidiasis.
  - Maculopapular rash, whether or not of allergic origin.
- **Very rare and at high doses or on long-term use:**
  - Moderate and transient elevation of transaminases and alkaline phosphatases.
  - Vaginal irritation."

09.3 Usage/prescription data

In France, this proprietary medicinal product is not sufficiently prescribed to appear in the prescription panels (EPPM-IMS).
The sales data (units - box of 12 tablets[9]) over the last five years are as follows:

2008	2009	2010	2011	2012 (estimated)
4919	4624	3230	4240	5001

09.4 Summary & discussion

Pivmecillinam is an antibiotic from the class of beta-lactams and related substances which is active against most enterobacteriaceae but not against gram-positive bacteria.
Recent clinical studies performed in Nordic countries (Sweden, Denmark), have shown its efficacy in acute uncomplicated cystitis, with more than 90% early bacteriological eradication after 7 days of treatment with a dosage of 200 mg x 2/day.[6] On the other hand, on shorter treatment (3 days) in a higher dosage (400 mg x 2/day, or even 400 x 3/day),[5,6] efficacy was less good, with percentages of early bacteriological eradication varying from 69% to 84% depending on the study. These results confirm those of earlier studies[7,8] showing that treatment with pivmecillinam for 3 days was less effective than 7 days' treatment or than 3 days' treatment with norfloxacin (fluoroquinolone). Consequently, the authors recommend using pivmecillinam (200 mg x 2/day) in 7 days' treatment.
However, since these studies were performed in Nordic countries, their results are not completely transferrable to clinical practice in France because of the current level of resistance to pivmecillinam in France of *E. coli*, the main organism found in community-acquired urinary tract infections.

The safety data from clinical studies and the available pharmacovigilance data confirm the good safety of pivmecillinam.

[9] Data supplied by the company (community sales)

No study:

- has compared pivmecillinam with the antibiotics currently recommended in France in the management of urinary tract infections.
- has assessed pivmecillinam in cases of acute, complicated cystitis, pyelonephritis or prostatitis; urinary tract infections due to enterobacteriaceae producing broad-spectrum beta-lactamases whereas *in vitro* data show good activity of pivmecillinam against some of these organisms.

09.5 Programme of studies

Not applicable.

010 THERAPEUTIC USE

- Pivmecillinam is a possible option in cases of acute uncomplicated cystitis in women, in view of:
  - its proven efficacy in this clinical setting, with a satisfactory safety profile,
  - its activity on most enterobacteriaceae, including on certain strains producing extended-spectrum beta-lactamases (ESBL),
  - the lack of cross-resistance to other beta-lactams,
  - the ability to use it during pregnancy,
  - the interest in limiting the use of fluoroquinolones and sulfonamides because of the risk of resistance development.

However, reduced efficacy, particularly microbiological, has been described when it is used in short-term treatment for 3 days. In addition, uncertainties remain about the optimal dosage and duration (from 6 to 8 days in most cases but possibly from 3 to 4 days in current, uncomplicated conditions) of treatment with this antibiotic, and about the current level of *E. coli* resistance to pivmecillinam in France.

- Pivmecillinam has no place in therapeutic use to treat acute complicated cystitis, pyelonephritis or acute prostatitis, given the absence of any proof of efficacy in these types of infection.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

Urinary tract infections are very common diseases, constituting the second commonest site of bacterial infection after the respiratory system. These infections are most often harmless, but if in a parenchymal location (pyelonephritis, prostatitis) they may be accompanied by severe sepsis and be life-threatening.

This proprietary medicinal product is intended as curative therapy.

The efficacy/adverse effects ratio for SELEXID is moderate in the treatment of acute uncomplicated cystitis in women. In other clinical situations (acute complicated cystitis, pyelonephritis and acute prostatitis), its efficacy/adverse effects ratio has not been established.
It is a first-line therapy for acute uncomplicated cystitis in women.
There are treatment alternatives.

- Public health benefit

  Given their frequency, urinary tract infections, even though they are in most cases not severe, are a moderate public health burden.
  Management of these infections is not a public health need. However, improving the proper use of antibiotics is one of the central themes of the 2007-2010 Antibiotics Plan, and having treatment alternatives in the management of infections in general practice and in hospitals is part of this public health objective.
  In the context of complicated urinary tract infections, and of infections with resistant organisms, and in particular with enterobacteriaceae ESBLs, in the absence of data in this indication, the impact of SELEXID on morbidity and mortality has not been proven and the public health benefit cannot be quantified.
  In acute uncomplicated cystitis in women, the impact of SELEXID on morbidity is moderate. In the absence of data, the impact on the quality of life has not been demonstrated.
  In addition, the duration of treatment compared with the short treatments available in this indication could have a negative impact on compliance, with a risk of resistance development.
  SELEXID is not expected to have any impact on the organisation of healthcare.
  Moreover, the applicability to French practice of the data presented is debatable, mainly because of the age and location of the studies (Nordic countries), the lack of any comparison with the antibiotics currently recommended in France, the uncertainty about the dosage and the optimal duration of treatment and the current level of *E. coli* resistance to pivmecillinam in France.
  Thus, SELEXID only partly meets the therapeutic need but does represent an alternative in this indication.
  In conclusion, in acute, uncomplicated lower urinary tract infections in young women, SELEXID will not benefit public health.

Consequently, given the current state of the dossier, the Committee believes that the actual benefit of SELEXID is:

- **Substantial only in the case of acute uncomplicated cystitis in women.**
- **Insufficient for reimbursement for hospital use in view of the treatment alternatives available for other urinary tract infections: acute complicated cystitis, pyelonephritis and acute prostatitis.**

011.2 Improvement in actual benefit (IAB)

Given the absence of any comparative studies versus the alternatives currently used in France in the treatment of community-acquired urinary tract infections, the Committee considers that the proprietary medicinal product SELEXID does not provide any improvement in actual benefit (IAB V, nonexistent) in the management of acute uncomplicated cystitis in women.

011.3 Target population

Urinary tract infections are a heterogeneous group of infections of the urinary system or its adnexae, the epidemiology of which is not well known.
The estimated incidence[3] varies from 4 to 6 million cases a year in France, the large majority of which are of cystitis. The incidence is higher in women than in men.
In the absence of accurate epidemiological data, the number of patients likely to receive SELEXID 200 mg is difficult to assess, but it is rather limited, given the fairly low percentage of patients eligible for this treatment (women with acute uncomplicated cystitis with organisms sensitive to pivmecillinam).

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in the treatment of community-acquired urinary tract infections only in cases of acute uncomplicated cystitis in women.

Given the broad indication of the Marketing Authorisation for this antibiotic (*"urinary tract infections with organisms sensitive to pivmecillinam"* with no distinction between upper or lower, uncomplicated or complicated), the Committee recommends revision of the Marketing Authorisation for pivmecillinam so as to better target the population likely to benefit from this antibiotic and to clarify the duration of use and dosage which vary greatly between studies. The Committee will consider revising its opinion according to the conclusions reached.

- **Proposed reimbursement rate: 65%**

- **Packaging**

The dosage and the optimal duration of treatment must be clarified so that the packaging can be adapted to the prescription conditions.