HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

21 July 2010

IZILOX 400 mg/250 ml, solution for infusion
B/5 (CIP code: 576 926-0)
B/12 (CIP code: 576 927-7)
B/1 (CIP code: 576 928-3)
B/5 (CIP code: 576 930-8)

Applicant: BAYER SANTE

moxifloxacin
ATC code: J01MA14

List I
Reserved for hospital use

Date of Marketing Authorisation (mutual recognition procedure): 18 March 2010

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Moxifloxacin

1.2. Indication

"IZILOX is indicated for the treatment of:

community acquired pneumonia
complicated skin and skin structure infections

Moxifloxacin should only be used for the treatment of community acquired pneumonia and complication skin and skin structure infections when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

Consideration should be given to official guidance on the appropriate use of antibacterial agents."

1.3. Dosage and method of administration

"400 mg moxifloxacin, infused once daily.
Initial intravenous treatment may be followed by oral treatment with moxifloxacin 400 mg tablets, when clinically indicated.
In clinical studies most patients switched to oral therapy within 4 days (community acquired pneumonia) or 6 days (complicated skin and skin structure infections). The recommended total duration of intravenous and oral treatment is 7 - 14 days for community acquired pneumonia and 7 - 21 days for complicated skin and skin structure infections.
Renal and/or hepatic impairment
No adjustment of dosage is required in patients with mild to severely impaired renal function or in patients on chronic dialysis i.e. haemodialysis and continuous ambulatory peritoneal dialysis.
There is insufficient data in patients with impaired liver function.
Other special populations
No adjustment of dosage is required in the elderly and in patients with low bodyweight.
Children and adolescents
Moxifloxacin is contraindicated in children and growing adolescents.
Efficacy and tolerance of moxifloxacin in children and adolescents have not been established.
Method of administration
For intravenous use: constant infusion over 60 minutes.
If medically indicated the solution for infusion can be administered via a T-tube, together with compatible infusion solutions".

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

J : anti-infectives for systemic use
J01 : antibacterials for systemic use
J01M : quinolone antibacterials
J01MA : fluoroquinolones
J01MA14 : moxifloxacin

2.2. Medicines in the same therapeutic category

2.2.1. Strictly comparable medicines in the same therapeutic category

Other antipneumococcal fluoroquinolone:

- levofloxacin: TAVANIC 5 mg/ml solution for infusion, and 500 mg tablet
  (no Marketing Authorisation in complicated skin and skin structure infections)

2.2.2. Not-strictly comparable medicines in the same therapeutic category

Other fluoroquinolones for systemic use

- ofloxacin: OFLOCET and its generics
- ciprofloxacin: CIFLOX and its generics

2.3. Medicines with a similar therapeutic aim

These are antibiotics with the same therapeutic indication, the same spectrum of antimicrobial activity or a similar spectrum, for systemic use.

2.3.1. In the indication "community acquired pneumonia"

Antibiotic (INN)	Trade name
Aminopenicillin	
Amoxicillin	several presentations
Aminopenicillin + beta lactamase inhibitor	
Amoxicillin + clavulanic acid	AUGMENTIN, CIBLOR
Piperacillin-tazobactam	TAZOCILLINE
Carbapenem	
Imipenem	TIENAM
Third-generation cephalosporin for injection: C3G	
Ceftriaxone	ROCEPHINE
Cefotaxime	CLAFORAN
Cefepime	AXEPIM
Macrolides	
Erythromycin	several presentations
Spiramycin	ROVAMYCINE
Josamycin	JOSACINE
Roxithromycin	CLARAMID, RULID
Clarithromycin	NAXY, ZECLAR
Dirithromycin	DYNABAC
Ketolides	
Telithromycin	KETEK
Synergistin	
Pristinamycin	PYOSTACINE
Cycline	
Doxycycline	VIBRAMYCINE

2.3.2. In the indication “complicated skin and skin structure infections”

Antibiotic (INN)	Trade name
Penicillinase-sensitive penicillin	
Penicillin G	EXTENCILLINE
Penicillin V	ORACILLINE
Aminopenicillin	
Amoxicillin	several presentations
Penicillin M	
Cloxacillin	ORBENINE
Oxacillin	BRISTOPEN
Aminopenicillin + beta lactamase inhibitor	
Amoxicillin + clavulanic acid	AUGMENTIN, CIBLOR
Piperacillin-tazobactam	TAZOCILLINE
Macrolide-related agents: lincosamides-synergistins	
Pristinamycin	PYOSTACINE
Quinupristin-dalfopristin	SYNERCID
Clindamycin	DALACINE
Glycopeptide	
Teicoplanin	TARGOCID
Vancomycin	No princeps
Oxazolidinone	
Linezolid	ZYVOXID
Cyclic lipopeptide	
Daptomycin	CUBICIN
Tetracycline	
Tigecycline	TYGACIL

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

3.1.1. In the indication "community acquired pneumonia"

The clinical dossier is based mainly on three phase III controlled studies which compared sequential administration (intravenous followed by possible oral administration) of moxifloxacin versus beta-lactam/fluoroquinolone bitherapy (study 11215) or beta-lactam/macrolide bitherapy (studies 10507 and 200036) in adult patients with acute community-acquired pneumonia (ACP) necessitating hospitalisation.

- Methods

Type of study	Treatment regimen	Number of patients
Study 11215 (MOTIV)[1] Controlled, randomised, double-blind, non-inferiority study (delta threshold 10%). Location: Europe, South Africa, Latin America (January 2004 - July 2005)	**moxifloxacin i.v./p.o.**: 400 mg x 1/day **ceftriaxone i.v.** (2 g/day) + **levofloxacin** (500 mg x2/day by i.v. then oral route) **Duration of treatment**: 7 to 14 days	**N = 733** Moxifloxacin: 368 Comparator: 365
Study 10507 (MOXIRAPID)[2] Controlled, randomised, open, non-inferiority study (delta threshold 15%). Location: Europe (December 2001 - March 2003)	**moxifloxacin i.v./p.o.**: 400 mg x 1/day **ceftriaxone i.v.** (2 g 1x/day) **± erythromycin i.v.** (1 g x 3/day or 4/day) **Duration of treatment**: 7 to 14 days	**N = 397** Moxifloxacin: 200 Comparator: 197
Study 200036 (TARGET)[3] Controlled, randomised, open, non-inferiority study (delta threshold 10%). Location: Europe, South Africa, Russia (February 1999 - May 2000)	**moxifloxacin i.v./p.o.**: 400 mg 1x/day **amoxicillin/clavulanic acid** (1000/200 mg i.v. then 500/125 mg p.o. x 3/day) **± clarithromycin** (500 mg x 2/day by i.v. then oral route) **Duration of treatment**: 7 to 14 days	**N = 628** Moxifloxacin: 306 Comparator: 322

The non-inclusion criteria included, in addition to the contraindications of moxifloxacin (notably congenital or acquired prolongation of the QT interval), patients with a lung abscess, purulent pleurisy or at risk of inhalation pneumonia and an underlying bronchopulmonary disease (bronchopulmonary cancer, diffuse dilation of the bronchi, cystic fibrosis, etc.).

Primary efficacy endpoint: clinical success defined as "complete resolution of the clinical signs and symptoms of infection or clinically significant improvement such that another antibiotic therapy was no longer necessary". This endpoint was evaluated 4 to 14 days after the end of the treatment in the MOTIV study, 5 to 20 days in the MOXIRAPID study, and 5 to 7 days in the TARGET study.

[1] Torres A et al. Moxifloxacin Monotherapy Is Effective in Hospitalized Patients with Community-Acquired Pneumonia: The MOTIV Study—A Randomized Clinical Trial. Clin Infect Dis. 2008 May 15;46(10):1499-509.

[2] Welte T. et al. Treatment with sequential intravenous or oral moxifloxacin was associated with faster clinical improvement than was standard therapy for hospitalized patients with community-acquired pneumonia who received initial parenteral therapy. Clin Infect Dis. 2005 Dec 15;41(12):1697-705. Epub 2005 Nov 10.

[3] Finch R. et al. Randomized controlled trial of sequential intravenous (i.v.) and oral moxifloxacin compared with sequential i.v. and oral co-amoxiclav with or without clarithromycin in patients with community-acquired pneumonia requiring initial parenteral treatment. Antimicrob Agents Chemother. 2002 Jun;46(6):1746-54.

- Results

The main demographic and medical characteristics were similar in the various treatment groups (PP population). The mean age of the patients included was between 55 and 65 years, depending on the study.
In the MOTIV study, which included only patients with ACP of class[4] III to V, most of the patients (90%) had ACP of class III or IV.
In the MOXIRAPID study, 56% of the patients had class I to II ACP, 27% class III, and 16% class IV. Only 1 patient in each group had class V ACP.
In the TARGET study, 50% of the patients had ACP that was deemed severe[5].
The number of patients with severe ACP admitted to an intensive care unit prior to initiation of the study therapy was small (approximately 10% in the MOTIV and MOXIRAPID studies and 2% in the TARGET study).
Streptococcus pneumoniae was the most frequently isolated pathogenic agent, and most of the strains were sensitive to penicillin. Infections caused by atypical microorganisms (*M. pneumoniae*, *Chlamydia spp.*, *L. pneumophila*) were limited.
The total duration of the treatment (intravenous followed by possible oral therapy) was 7 to 14 days.
The results for the primary efficacy endpoint are shown in Table 1. Non-inferiority was demonstrated in the various studies (lower limit of the confidence interval of the difference > -10%). It should be noted that the dosage of amoxicillin/clavulanic acid p.o. used in the TARGET study (0.5 g x 3/day) is lower than that recommended in practice (1 g x 3/day), which limits the value of the results of this study.

Table 1: Rates of clinical success at the end of the treatment

	Treatment groups		Difference [95% CI]
Study 11215 (MOTIV)	**moxifloxacin i.v./p.o.**	**ceftriaxone i.v. ± levofloxacin i.v./p.o.**	
PP population, n/N (%)	253/291 (86.9)	250/278 (89.9)	[-8.1; 2.2] *
ITT population, n/N (%)	293/368 (79.6)	306/365 (83.8)	[-9.7;1.4]
Study 10507 (MOXIRAPID)	**moxifloxacin i.v./p.o.**	**ceftriaxone i.v. ± erythromycin i.v.**	
PP population, n/N (%)	138/161 (85.7)	135/156 (86.5)	[-7.9; 7.1] **
ITT population, n/N (%)	150/200(75.0)	140/197(71.1)	[-4.7;12.2]
Study 200036 (TARGET)	**moxifloxacin i.v./p.o.**	**amoxicillin/clavulanic acid i.v./p.o. ± clarithromycin i.v./p.o.**	
PP population, n/N (%)	241/258 (93.4)	239/280 (85.4)	[2.9;13.2] *
ITT population, n/N (%)	243/301 (80.7)	242/321 (75.4)	[-0.1;12.3]

* delta non-inferiority threshold = 10% ** delta non-inferiority threshold = 15%

The rates of bacteriological success (eradication or presumed eradication) were of the same order depending on the study, though the numbers investigated (microbiologically evaluable population)[6] are too small to permit a robust interpretation of the results:
MOTIV study: 83.3% (45/54) in the moxifloxacin group *versus* 85.1% (46/54) in the comparator group, 95% CI = [-15.4; 11.8].
MOXIRAPID study: 82.1% (23/28) in the moxifloxacin group *versus* 83.9% (26/31) in the comparator group, 95% CI = [-23.2%; 14.6%].

[4] Severity of pneumonia according to the Fine score (PSI): Recommendations: Classes I to II: outpatient; Class III: observation; Classes IV-V: hospitalisation.

[5] Criteria of the American Thoracic Society . "*To meet the definition of severe CAP the patients had to have at least one of the following: a respiratory rate of _30 breaths/min, hypoxemia with a partial oxygen pressure of _8 kPa (60 mm Hg), a need for mechanical ventilation, diastolic blood pressure _60 mm Hg, a chest X ray showing bilateral or multilobar involvement, or a requirement for treatment with vasopressors for more than 4 h*".

[6] patients with a bacteriologically documented infection for whom culturing of the pulmonary samples and/or blood cultures led to the isolation of one or more pathogenic microorganisms.

TARGET study: 93.7% (60/64) *versus* 81.7% (58/71), 95% CI = [1.2; 22.9].

3.1.2. In the indication "complicated skin and skin structure infections"

The clinical dossier is based mainly on three studies which compared sequential administration (intravenous followed by possible oral administration) of moxifloxacin with that of a beta-lactam (amoxicillin-clavulanic acid or piperacillin-tazobactam), in hospitalised adult patients with a complicated skin and skin structure infection[7].

- Study methods

Type of study	Treatment regimen	Number of patients
Study 10279[8] Controlled, randomised, open, non-inferiority study (delta threshold 10%). Location: Europe, Israel, Asia, Latin America, South Africa (April 2001 - April 2002)	**moxifloxacin i.v./p.o.**: 400 mg x 1/day **amoxicillin/clavulanic acid** (1000/200 mg i.v. then 500/125 mg p.o. x 3/day) **Duration of treatment**: 7 to 21 days	N = 804 moxifloxacin: 406 Comparator: 397
Study 100273[9] Controlled, randomised, double-blind, non-inferiority study (delta threshold 15%). Location: North America + Latin America (December 2000 - July 2003)	**moxifloxacin i.v./p.o.**: 400 mg 1x/day **piperacillin/tazobactam i.v.** (3 g/375 mg x 4/day) then **amoxicillin/clavulanic acid p.o.** (800 mg/114 mg x 2/day) **Duration of treatment**: 7 to 14 days	N = 601 moxifloxacin: 298 Comparator: 303
Study 11974* Controlled, randomised, double-blind, non-inferiority study (delta threshold 10%). Location: Europe, Israel, South Africa, Russia (September 2006 - June 2008)	**moxifloxacin i.v./p.o.**: 400 mg x 1/day **piperacillin/tazobactam i.v.** (4 g/500 mg x 3/day) then **amoxicillin/clavulanic acid p.o.** (875/125 mg x 2/day) **Duration of treatment**: 7 to 21 days	N = 803 moxifloxacin: 426 Comparator: 377

*unpublished study not included in the Marketing Authorisation file

Primary efficacy endpoint: clinical success defined as "complete resolution of the clinical signs and symptoms of infection or clinically significant improvement such that another antibiotic therapy was no longer necessary". This endpoint was evaluated 14 to 28 days after the end of the treatment in studies 10279/11974 and 10 to 42 days in study 100273.

- Results

The demographic and medical characteristics were similar in the various treatment groups. The mean age of the patients was approximately 50 years (54 to 69% men).
The main infections treated were abscesses and diabetic foot infections (50% in studies 10279 and 100273 and 79% in study 11974). The other types of infections were a complication of erysipelas (28.1% in study 10279) or "cellulite" (24% in study 100273). The number of patients with severe skin infections, such as necrotizing fasciitis (8.9% in study 10279), was very limited.
The principal comorbidity factors were diabetes and peripheral vascular disease.
Staphylococcus aureus was the most frequently isolated microorganism, and most of the strains were sensitive to methicillin (Table 2).

[7] The complication criteria (according to the FDA): an infection of the deep soft tissues or requiring surgical intervention, pre-existing skin lesions, any underlying disease the effects of which could affect release of the drug at the lesion or which could induce an immunological response or prevent healing.
[8] Vick-Fragoso R. et al. Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections. Infection. 2009;37:407-17. Epub 2009 Sep 18.
[9] Giordano P. et al. Sequential intravenous/oral moxifloxacin versus intravenous piperacillin-tazobactam followed by oral amoxicillin-clavulanate for the treatment of complicated skin and skin structure infection. International Journal of Antimicrobial Agents 2005;26:357–365

Table 2: Most frequently isolated microorganisms (Population: patients valid for "per-protocol" analysis with positive initial bacteriological samples)

Microorganism	Study	Moxifloxacin n/N (%)	Comparators n/N (%)
Gram-positive aerobes			
Staphylococcus aureus	100273 10279 11974	64/119 (53.8) 59/167 (35.3) 175/268 (65.3)	59/118 (50.0) 78/172 (45.3) 171/243 (70.4)
Streptococcus pyogenes	100273 10279 11974	18/119 (15.1) 15/167 (9.0) 36/268 (13.4)	12/118 (10.2) 9/172 (5.2) 24/243 (9.9)
Streptococcus agalactiae	100273 10279 11974	13/119 (10.9) 9/167 (5.4) 31/268 (11.6)	25/118 (21.2) 17/172 (9.9) 13/243 (5.3)
Enterococcus faecalis	100273 10279 11974	18/119 (15.1) 16/167 (9.6) 61/268 (22.8)	12/118 (10.2) 11/172 (6.4) 50/243 (20.6)
Gram-negative aerobes			
Escherichia coli	100273 10279 11974	8/119 (6.7) 30/167 (18.0) 58/268 (21.6)	12/118 (10.2) 20/172 (11.6) 55/243 (22.6)
Klebsiella pneumoniae	100273 10279 11974	6/119 (5.0) 5/167 (3.0) 14/268 (5.2)	7/118 (5.9) 2/172 (1.2) 9/243 (3.7)
Proteus mirabilis	100273 10279 11974	5/119 (4.2) 11/167 (6.6) 8/268 (3.0)	6/118 (5.1) 10/172 (5.8) 9/243 (3.7)
Enterobacter cloacae	100273 10279 11974	4/119 (3.4) 6/167 (3.6) 20/268 (7.5)	2/118 (1.7) 4/172 (2.3) 15/243 (6.2)
Pseudomonas aeruginosa	100273 10279 11974	5/119 (4.2) 3/167(1.8) 9/268 (3.4)	11/118 (9.3) 6/172 (3.5) 4/243 (1.6)
Gram-negative anaerobes			
Bacteroides species	100273 10279 11974	3/119 (2.5) 2/167 (1.2) 26/268 (9.7)	6/118 (5.1) 0/172 (0.0) 19/243 (7.8)

N = number of patients with at least one microorganism; n = number of patients with the microorganism concerned

The total duration of the treatment (intravenous followed by possible oral therapy) was 7 to 21 days.

The results for the primary efficacy endpoint are shown in Table 3. Non-inferiority was demonstrated in the various studies at the predetermined thresholds.

Table 3: Clinical success at the end of the treatment (primary endpoint)

	Treatment groups		Difference [95% CI]
Study 10279	**Moxifloxacin i.v./p.o.**	**amoxicillin/clavulanic acid i.v./p.o.**	
PP population, n/N (%)	254/315 (80.6)	268/317 (84.5)	[-9.4;2.2] *
ITT population, n/N (%)	295/406 (72.7)	297/397 (74.8)	[-7.6;4.3]
Study 100273	**moxifloxacin i.v./p.o.**	**piperacillin/tazobactam i.v. amoxicillin/clavulanic acid p.o.**	
PP population, n/N (%)	143/180 (79.4)	153/187 (81.8)	[-12.0; 3.3] **
ITT population, n/N (%)	166/298 (55.7)	169/303 (55.8)	[-7.5;7.5]
Study 11974	**moxifloxacin i.v./p.o.**	**piperacillin/tazobactam i.v. amoxicillin/clavulanic acid p.o.**	
PP population, n/N (%)	320/361 (88.6)	275/307 (89.6)	[-5.3; 3.9] *
ITT population, n/N (%)	350/426 (82.2)	305/377 (80.9)	[-3.8; 6.3]

* delta non-inferiority threshold = 10%
** delta non-inferiority threshold = 15%

The clinical and bacteriological success rates in the patients with a microbiologically documented infection are presented in Table 4.

Table 4: Clinical and bacteriological success rates in the patients with a microbiologically documented infection (secondary endpoints)

Population	**Study**	**Moxifloxacin**		**Comparator**		Difference [95% CI]
		n/N	**%**	**n/N**	**%**	
Clinical success						
PP population	10279	126/167	(75.4)	137/172	(79.7)	[-12.0%; 5.8%]
	100273	92/119	(77.3)	97/119	(81.5)	[-15.5%; 4.2%]
	11974	233/268	(86.9)	215/243	(88.5)	[-7.5%; 3.4%]
ITT population	10279	145/219	(66.2)	140/208	(67.3)	[-8.8%; 8.9%]
	100273	100/194	(51.5)	104/177	(58.8)	[-16.1%; 3.1%]
	11974	254/313	(81.2)	234/290	(80.7)	[-5.8 %; 6.1%]
Bacteriological success (eradication or presumed eradication)						
PP population	10279	127/167	(76.1)	140/172	(81.4)	[-13.0%; 4.4%]
	100273	92/119	(77.3)	96/118	(81.4)	[-14.8%. 5.2%]
	11974	226/268	(84.3)	212/243	(87.2)	[-9.3%; 2.2%]
ITT population	10279	147/219	(67.1)	144/208	(69.2)	[-9.7%; 7.8%]
	100273	100/194	(51.5)	105/176	(59.7)	[-17.1%; 2.3%]
	11974	248/313	(79.2)	229/290	(79.0)	[-6.6%; 5.7%]

3.2. Adverse effects

The adverse events observed most frequently (<10%) in the clinical trials were gastrointestinal (nausea, vomiting, diarrhoea) and hepatic (increase in transaminases). QT prolongation (already known from the oral form) was also demonstrated with the intravenous form. The SPC states that the magnitude of this prolongation may increase with increasing plasma concentrations due to rapid intravenous infusion (see SPC: special warnings, contraindications, etc.).

Clinical experience (according to SPC)
Other than nausea and diarrhoea, the frequency of all the adverse events observed in the clinical trials with moxifloxacin administered at a dose of 400 mg per day p.o. or i.v. was less than 3%.

The following adverse effects were observed at a higher frequency in the subgroup of patients treated by the intravenous route, with or without subsequent oral therapy:

Common (>1/100 <1/10):
- increase in gamma GT
Uncommon: (>1/1000 <1/100)
- ventricular tachyarrhythmias, hypotension, oedema, antibiotic-associated colitis (including pseudomembranous colitis, associated in very rare instances with potentially life-threatening complications; seizures including *grand mal* seizures, hallucinations, renal impairment (including an increase in urea and creatinine), renal failure (see section 4.4 of the SPC).

3.3. Conclusion

In the indication "community acquired pneumonia", the clinical trials (MOTIV, MOXARAPID, and TARGET studies) carried out in hospitalised patients showed the clinical efficacy of moxifloxacin (intravenous followed by possible oral administration) to be non-inferior to that of a beta lactam/fluoroquinolone bitherapy (ceftriaxone i.v. + levofloxacin i.v./p.o.) or a beta lactam/macrolide bitherapy (amoxicillin/clavulanic acid i.v./p.o. ± clarithromycin i.v./p.o.; or ceftriaxone i.v. ± erythromycin i.v.), with clinical success rates ranging from 85 to 90% (PP analysis).
However, these studies included a very small number of patients with severe ACP requiring hospitalisation in an intensive care/critical care unit, which limits the applicability of the results in this population of interest.

In the indication "complicated skin and skin structure infections[10]", the clinical trials (100273, 10279, and 11974) carried out in hospitalised adult patients showed the clinical efficacy of moxifloxacin (i.v./p.o.) to be non-inferior to that of a beta lactam (amoxicillin-clavulanic acid or piperacillin-tazobactam), with clinical success rates ranging from 80 to 90% (PP analysis).
However, the main infections treated were abscesses and diabetic foot infections, with a predominance of gram-positive aerobic cocci (staphylococci sensitive to methicillin in the majority of cases), suggesting that the infections were community acquired.
Clinical efficacy has thus not been established in patients with skin infections that are severe (e.g. bacterial dermohypodermitis and necrotising fasciitis) and/or due to multiresistant microorganisms. Thus, a warning was inserted in the SPC, mentioning the inadequacy of the data, particularly in regard to the treatment of severe burns infections, fasciitis, major abscesses, diabetic foot infections with osteomyelitis, and in the case of infection with methicillin-resistant *Staphylococcus aureus* (*a resistance rate > 50% was reported for methicillin-resistant Staphylococcus aureus)*.

Tolerance: The data from the clinical trials and the PSURs did not bring to light any unexpected adverse effects relative to the effects already known for the oral form. The main risk associated with the use of the product is cardiac toxicity, QT prolongation in particular.

[10] The complication criteria (according to the FDA): an infection of the deep soft tissues or requiring surgical intervention, pre-existing skin lesions, any underlying disease the effects of which could affect release of the drug at the lesion or which could induce an immunological response or prevent healing.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

- *Community acquired pneumonia*

The conditions concerned by this proprietary product are immediately life-threatening or may cause fatal complications.

This proprietary product is intended as curative therapy.

The efficacy/adverse effects ratio for this medicinal product is high in infections of moderate severity (patients hospitalised in medical departments) – with the reservation associated with cardiac tolerance. In the more severe forms requiring hospitalisation in an intensive care or critical care unit, the efficacy/adverse effects ratio remains to be clarified.

There are treatment alternatives, including for multiresistant microorganisms.

This proprietary product is a second-line therapy, when it is considered inappropriate to use the antibiotic agents that are commonly recommended for the initial treatment of these infections.

Expected Public Health Benefit

The public health burden of acute community acquired pneumonia in the population of patients who are candidates for IZILOX therapy is low, in view of the probably limited number of patients concerned.

Providing new drugs to tackle the spread of pathogenic bacteria which have acquired mechanisms of resistance to antibiotics is a public health need.

In ACP, it is expected that IZILOX would have only a weak impact in regard to reduction of mortality in comparison with the other available therapies.

There is no guarantee that the experimental data can be carried over into actual practice, given that the patients included in the trials are not representative of those likely to receive IZILOX in practice. In the current state of knowledge, therefore, it has not been established that the public health need is met.

Consequently, it is not expected that IZILOX will benefit public health benefit in this indication.

The actual benefit of this proprietary product is substantial, in view of its effect on the pneumococcus (the main microorganism involved in pneumonia), including strains resistant to penicillin and macrolides, provided that the contraindications and special warnings and precautions for use are adhered to.

- *Complicated skin and skin structure infections*

Complicated skin and skin structure infections comprise a highly diverse array of clinical entities, which vary in their conditions of occurrence, therapeutic management, and prognosis, ranging from ulcer, infected wounds, abscesses, erysipelas, and diabetic foot to the most severe forms of bacterial dermohypodermitis and necrotizing fasciitis.

This proprietary product is intended as curative therapy.

The efficacy/adverse effects ratio for this medicinal product in skin infections that are severe and/or due to multiresistant microorganisms has not been established.

There are treatment alternatives, including for multiresistant microorganisms.

This medicinal product does not have a place in therapeutic use, in view of the inadequate documentation of clinical efficacy and the reservations in regard to cardiac tolerance.

Public Health Benefit

The public health burden of complicated skin and skin structure infections in the population of patients who are candidates for IZILOX therapy is low, in view of the probably limited number of patients concerned.

Providing new drugs to tackle the spread of pathogenic bacteria which have acquired mechanisms of resistance to antibiotics is a public health need.

However, in complicated skin and skin structure infections, no additional impact in terms of reduction of morbidity is expected relative to the treatments used in current practice.

There is no guarantee that the experimental data can be carried over into actual practice, given that the patients included in the trials are not representative of those likely to receive IZILOX in practice.

IZILOX does not meet the identified public health need.

Consequently, it is not expected that IZILOX will benefit public health benefit in this indication.

The actual benefit of this medicinal product is not sufficient to justify its being reimbursed by National Health Insurance in view of the existing treatments.

4.2. Improvement in actual benefit (IAB)

- *Community acquired pneumonia*

In view of the following:

- the non-optimal level of evidence in regard to the demonstration of efficacy and tolerance in severe community acquired pneumonia requiring hospitalisation in an intensive care/critical care unit,
- the reservations regarding cardiac tolerance, particularly prolongation of QT,
- and doubts over whether the results of the clinical trials can be carried over into real life,

the Committee is of the view that the proprietary product IZILOX does not bring an improvement in actual benefit (IAB V) in the management of “community acquired pneumonia”.

- *Complicated skin and skin structure infections*

Not applicable

4.3. Therapeutic use

4.3.1. In the indication “acute community acquired pneumonia” (ACP)

Management of ACP

Acute community acquired pneumonia is an infection in which the causative organism is acquired outside hospital. It is divided into 4 subgroups on the basis of epidemiological and clinical criteria: outpatient, < 65 years of age, without comorbidity; outpatient, > 65 years of age and/or with comorbidity; patient needing to be hospitalised; patient hospitalised in intensive care/critical care. The severity of the pneumonia is also established on the basis of clinical and paraclinical data. The aetiology and management vary according to the subgroup to which the patient belongs.

Antibiotic therapy of a probabilistic nature is the norm, both in the outpatient and the hospital setting. The patient should be systematically re-evaluated after 48-72 h.

The antibiotic therapy should take account of:

- the bacteria most frequently implicated and/or responsible for high mortality:
  - *S. pneumoniae, M. pneumoniae* in outpatients
  - *S. pneumoniae, L. pneumophila* for severe ACP
- the lower sensitivity of *S. pneumoniae* to penicillin (choice and dosage of ß-lactam), and, in particular, the resistance to macrolides;
- the patient’s risk factors.

Place of anti-pneumococcal fluoroquinolones (levofloxacin, moxifloxacin)

Generally speaking, these substances should be reserved for second-line treatment or for particular areas. Caution must be exercised in regard to their use in institutions (risk of transmission of resistant strains) and in elderly persons receiving systemic corticosteroid therapy (increased risk of tendinopathy). Because of the very good bioavailability of systemic quinolones, oral administration should be preferred.

Antipneumococcal fluoroquinolones (APFQ):

- do not have a place in first-line treatment of ACP in healthy outpatients, without signs of severity or morbidity;
- can be used in these same patients in cases where a properly conducted initial therapy has failed. However, recent previous prescription (within the last three months), irrespective of whether the initial indication was APFQ or not, poses a risk of selection of less sensitive strains and represents a reservation in regard to their use. Their repeated prescription to the same patient is thus not recommended.
- can be proposed as first-line therapy, in outpatients with concomitant disease(s), the elderly, or patients hospitalised in medical departments if infection with intracellular or related microorganisms is suspected;
- can be used in critical care, but in combination with an injectable broad-spectrum ß-lactam;
- must be avoided if underlying tuberculosis is suspected, on account of their antitubercular activity.

Moxifloxacin is contraindicated: in patients with congenital or acquired QT prolongation, disturbances of the water and electrolyte balance, in particular uncorrected hypokalaemia, clinically significant bradycardia, left ventricular failure, or a history of rhythm disorders on account of the risk of ventricular arrhythmia including torsades de pointes. It is also contraindicated in cases of severe hepatic impairment (Child Pugh class C) and in patients with transaminase levels 5 times higher than normal.

The updated national recommendations on antibiotic therapy of ACP[11] position moxifloxacin (i.v. and p.o.) as second-line therapy only and state that, if an APFQ is used, levofloxacin should preferably be employed, whether this is in hospitalised patients without signs of severity or in hospitalised patients in critical care.

4.3.2. In the indication “complicated skin and skin structure infections”

The usual treatment generally involves the use of antibiotics appropriate to the identified or likely bacteria. There are numerous possible choices, depending on the bacteria and their level of resistance.

IZILOX i.v. does not have a place in therapeutic use on account of the inadequate documentation of clinical efficacy in indications that are severe and/or due to multiresistant bacteria and on account of the reservations in regard to cardiac tolerance.

[11] Clarification: Systemic antibiotic therapy in lower respiratory tract infections in adults. Afssaps [French Health Product Safety Agency] – 13 July 2010. http://www.afssaps.fr/Infos-de-securite/Mises-au-point/Antibiotherapie-par-voie-generale-dans-les-infections-respiratoires-basses-de-l-adulte-Mise-au-point

4.4. Target population

4.4.1. In the indication "acute community acquired pneumonia" (ACP)

In France, the annual incidence of ACP[12] ranges from 5/1000 to 12/1000, or approximately 400,000 to 600,000 patients per year.
Most of the patients are cared for on an outpatient basis.

As a guide, data from the Programme de médicalisation du système d'information [(PMSI [programme for clinical information systems]-MCO [medicine surgery obstetrics] - ATIH [national agency for information on hospitalisation] 2009 national database) for the year 2009 record 160,695 stays in hospital because of pneumopathy (ICD-10 codes: J13 to J18); in 61,370 of these stays the principal diagnosis was "*Pneumonia due to Streptococcus pneumoniae, Pneumopathy due to Haemophilus influenzae, Bacterial pnemopathies not otherwise specified, - ICD-10 codes: J13 to J15"*.

In practice, the number of patients likely to receive IZILOX i.v. will be limited on account of the fairly low percentage of patients who would be more particularly eligible for this treatment: adult patients requiring hospitalisation and initial antibiotic therapy by the intravenous route, for whom it is considered inappropriate to use the antibiotic agents that are commonly recommended.

4.4.2. In the indication "complicated skin and skin structure infections"

Not applicable

4.5. Transparency Committee recommendations

- The transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indication "*community acquired pneumonia"*.
- The Transparency Committee does not recommend inclusion on the list of medicines approved for hospital use and various public services in the indication "*complicated skin and skin structure infections*".

[12] E. Pilly. Maladies Infectieuses et Tropicales [Infectious and Tropical Diseases]. By the Collège des Universitaires de Maladies Infectieuses et tropicales [College of Professors of Infectious and Tropical Diseases]. 2008 edition.