HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

28 May 2008

CUBICIN 350 mg (daptomycin), powder for solution for infusion
Box containing 1 bottle (CIP: 567 219-3)

CUBICIN 500 mg (daptomycin), powder for solution for infusion
Box containing 1 bottle (CIP: 567 220-1)

Applicant: NOVARTIS PHARMA S.A.S

daptomycin

List I
Medicinal product for hospital use only

Marketing Authorisation (MA) date: 19 January 2006, amending the authorisation of 31 August 2007

European MA, centralised procedure

Reason for request: Inclusion on the list of medicines approved for use by hospitals in the extension of indication:

- **Right-sided infective endocarditis (RIE) due to *Staphylococcus aureus*. It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of the organism and should be based on expert advice.**
- ***Staphylococcus aureus* bacteraemia (SAB) when associated with RIE or with Complicated skin and soft-tissue infections (cSSTI).**

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

daptomycin

1.2. Background

CUBICIN is the first example of a new class of antibacterials: Cyclical lipopeptides with a bactericidal action.

1.3. Indication

“Cubicin is indicated for the treatment of the following infections in adults:

- Complicated skin and soft-tissue infections cSSTI.
- **RIE due to SAB. It is recommended that the decision to use daptomycin should take into account the antibacterial susceptibility of the organism and should be based on expert advice.**
- **SAB when associated with RIE or with cSSTI.**

Daptomycin is active against Gram positive bacteria only. In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, Cubicin should be co-administered with appropriate antibacterial agent(s).
Consideration should be given to official guidance on the appropriate use of antibacterial agents.”

1.4. Dosage

“Dosage

- cSSTI without concurrent SAB: The recommended dose is 4 mg/kg administered once every 24 hours for 7-14 days or until the infection is resolved.
- **cSSTI with concurrent SAB: The recommended dose is 6 mg/kg administered once every 24 hours. See below for dose adjustments in patients with renal insufficiency. The duration of therapy may need to be longer than 14 days in accordance with the perceived risk of complications in the individual patient.**
- **Known or suspected RIE due to SAB: The recommended dose is 6 mg/kg administered once every 24 hours. See below for dose adjustments in patients with renal insufficiency. The duration of therapy should be in accordance with available official recommendations.**

Renal insufficiency

Daptomycin is eliminated primarily by the kidney.

Due to limited clinical experience (see table and footnotes below) Cubicin should only be used in patients with any degree of renal insufficiency (Cr Cl < 80 ml/min) when it is considered that the expected clinical benefit outweighs the potential risk. The response to treatment and renal function should be closely monitored in all patients with some degree of renal insufficiency.

Table 1: Dose adjustments in patients with renal insufficiency by indication and creatinine clearance

Indication (1)	Creatinine clearance (1)	Dose recommendation (1)	Comments
cSSTI without S. aureus bacteraemia	≥ 30 ml/min	4 mg/kg once daily	See section 5.1 of SPC
	< 30 ml/min	4 mg/kg every 48 hours	(1, 2)
RIE or cSSTI associated with S. aureus bacteraemia	≥ 50 ml/min	6 mg/kg once daily	(3)

(1) The safety and efficacy of the dose interval adjustment has not been clinically evaluated and the recommendation is based on pharmacokinetic modelling data.

(2) The same dose adjustments, which are also based solely on modelling are recommended for patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Whenever possible, CUBICIN should be administered following the completion of dialysis on dialysis days

(3) There are insufficient data to support a dose recommendation for patients with RIE or cSSTI associated with SAB who have a creatinine clearance < 50 ml/min. There are no data available to support the efficacy of 4 mg/kg daily in patients with RIE or cSSTI associated with SAB whose creatinine clearance is between 30-49 ml/min or to support the use of 4 mg/kg every 48 hours in such patients whose creatinine clearance is < 30 ml/min.

Hepatic insufficiency

No dose adjustment is necessary when administering Cubicin to patients with mild or moderate hepatic insufficiency (Child-Pugh Class B). No data are available in patients with severe hepatic insufficiency (Child-Pugh Class C). Therefore caution should be exercised if CUBICIN is given to such patients.

Elderly patients

The recommended doses should be used in elderly patients except those with severe renal insufficiency. However, there are limited data on the safety and efficacy of daptomycin in patients aged > 65 years and caution should be exercised if CUBICIN is given to such patients.

Children and adolescents (< 18 years old)

Due to the lack of data on safety and efficacy CUBICIN is not recommended for use in children and adolescents (< 18 years of age).

Method of administration

Cubicin is given by intravenous infusion and administered over a 30 minute period."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

J: general anti-infectives for systemic use
J01: Antibacterials for systemic use
J01X: other antibacterials
J01XX: other antibacterials
J01XX09: daptomycin

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

Beta-lactam antibiotics, including semi-synthetic penicillins, are used to treat infection with methicillin-sensitive strains of Staphylococcus.
Glycopeptides, which include vancomycin and teicoplanin, may be used to treat infections involving methicillin-resistant Staphylococcus.
An **aminoside**, namely gentamicin, may also be used, in combination with semi-synthetic penicillins to treat infections involving methicillin-sensitive Staphylococcus, or in combination with vancomycin for infections with methicillin-resistant Staphylococcus.

2.3.1. Semi-synthetic penicillins

oxacillin:

- BRISTOPEN 500 mg and 1 g, powder and solvent for solution for injection
- OXACILLIN PANPHARMA 500 mg and 1 g, powder for solution for injection (IM, IV)

cloxacillin:

- ORBENIN 1 g/5 mL, powder and solution for solution for injection, IM or IV
- ORBENIN 250 mg and 500 mg, capsule
- CLOXACILLIN PANPHARMA 1 g, powder and solvent for solution for injection, IM

2.3.2. Glycopeptides

vancomycin:

- VANCOMYCIN MERCK 125 mg, 250 mg, 500 mg and 1 g, powder for solution for infusion
- VANCOMYCIN QUALIMED 500 mg and 1 g, powder for solution for infusion
- VANCOMYCIN SANDOZ 125 mg, 250 mg, 500 mg and 1 g, powder for solution for infusion

teicoplanin:

- TARGOCID 100 mg, 200 mg and 400 mg, lyophilisate and solution for parenteral use.

2.3.3. Aminoside

gentamicin:

- GENTALLINE 10, 40, 80, 160 mg, solution for injection and generics- GENTALLINE DAKOTA PHARMA
- GENTALLINE PANPHARMA

2.3.4. Other comparable products

According to the guidelines, cefamandole, rifampicin or other anti-Staphylococcus agent can be used in infective endocarditis, depending on the susceptibility of the organism.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The clinical dossier is based on an open-label controlled study (the DAP-IE-01-02 study)[1], with the objective to demonstrate non-inferiority of daptomycin (CUBICIN) in the treatment of bacteraemia or infective endocarditis involving SAB in comparison with "conventional"[2] treatment [semi-synthetic penicillin or vancomycin ± gentamicin]. CUBICIN was considered as non-inferior to the comparative therapy if the lower limit of the 95% confidence interval of the difference between the clinical success rates (CUBICIN – comparator therapy) was greater than -20%.

An adjudication committee of independent experts simultaneously evaluated, blindly and using set criteria, each patient's eligibility and response to treatment.

- **Population**

In order to be included in the study, patients (aged > 18 years) had tohave at least one documented positive blood culture for SAB done during the two days prior to the start of antibiotic therapy.

Each patient's eligibility was blindly evaluated by the independent experts committee based on the following criteria (modified Duke criteria):

Complicated RIE*: defined as definite or possible infective endocarditis (IE) with no predisposing lesions or infectious lesions of the mitral or aortic valves on echocardiography, in a patient with at least one of the following signs: extra-pulmonary location, MRSA, creatinine > 221 µmol/l*
Non-complicated RIE*: defined as definite or possible IE with no predisposing lesions or infectious lesions of the mitral or aortic valves on echocardiography, in a patient with MSSA, creatinine < 221 µmol/L and who does not have any signs of extra-pulmonary infection.*
Left-sided IE*: defined as definite IE or possible IE associated with predisposing or infectious lesions of the mitral or aortic valves, demonstrated on trans-oesophageal echocardiography.*
Complicated bacteraemia involving S. aureus with no IE*: defined as blood culture positive for SAB at least 2 days running, during the first 5 days of treatment, with no endocarditis but with signs of dissemination in the blood or infection of a retained prosthesis within 4 days.*

The following patients were not included: patients with heart valve prosthesis, those with creatinine clearance of less than 30 mL/min, osteomyelitis, bacteraemia involving multiple organisms or pneumonia.

- **Treatments**

Patients were randomised and received open-label treatment:

- either CUBICIN: 6 mg/kg, administered intravenously using a 30-minute infusion every 24 hours
- or the comparator therapy: vancomycin, 1 g/12 h as a 60-minute infusion (dose adjusted depending on the patient's renal function) or a semi-synthetic penicillin (oxacillin, cloxacillin, nafcillin, flucloxacillin) 2 g/4 h as a 15-minute infusion.

All patients in the standard-therapy group and all patients in the CUBICIN group having a left-sided infective endocarditis had to receive gentamicin treatment during the first 4 days of therapy (or until blood cultures were negative for 48 hours).
If the organism susceptibility was not known at randomisation, patient randomised to the standard-therapy group received vancomycin and if the organism was found to be sensitive, the patient's treatment was changed to a semi-synthetic penicillin.

[1] Fowler *et al.,* Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. NEJM, 2006, 355, 7: 653-665.
[2] Semi-synthetic penicillins are standard treatments for infection with methicillin-sensitive Staphylococcus. Vancomycin is used in patients infected with methicillin-resistant Staphylococcus. Combined treatment with an aminoside eliminates the organism slightly more quickly from vegetation or blood.

Minimum duration of therapy was between 10 and 42 days, depending onsigns of complications and the susceptibility of the isolated SAB strain.

Patients who responded to treatment (cure or improvement) by the end-of-therapy (EOT) visit were followed up for 42 days (culminating in the test-of-cure (TOC) visit).

- **Endpoints**

The primary endpoint was the **clinical response (clinical success or failure),** evaluated by the committee of independent experts during the TOC visit using the following criteria:

Clinical success: a patient who received at least one dose of antibiotic therapy defined in the protocol, who didnot receive any antibiotics prohibited by the protocol, was classified by the committee as a clinical success at the EOT visit and was judged cured or improved at the TOC visit, with a negative blood culture.

Failure: have at least one of the following criteria: to be classified as a failure by the committee at the EOT or TOC visit, to have persistent or recurrent bacteraemia or no blood culture at the TOC visit, to be dead, to receive protocol prohibited antibiotics , to prematurely discontinue per-protocol treatment.

Non-evaluable patients: patients classified neither as successes nor as failures, or who discontinued treatment for various reasons (patient lost to follow-up, change of therapy, etc).

- **Results**

Two hundred and thirty six (236) patients were randomised and treated: 120 in the CUBICIN group and 116 in the standard therapy group.

At baseline, the two groups had similar demographic and medical characteristics, except for the CUBICIN group with a larger proportion of patients who undergone a **surgical procedure within the 30 days before bacteraemia onset (40.8% versus 31.8%), who had pre-existing heart valve disease (13.3% versus 7.8%) or were HIV positive (6.7% versus <1%).** The most common underlying pathology was diabetes (more than a third of patients in each group). Systemic inflammatory response syndrome was observed in around 75% of cases.
Methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated in around 40% of cases in each treatment group.

The table below provides a breakdown of diagnoses made by the experts committee at the EOT evaluation.

Table 2: Sub-groups of diagnoses made by the independent experts committee (ITT population)

Final Diagnosis	Cubicin® N=120	Comparator* N=115	Total N=235
Complicated RIE	13 (10.8%)	12 (10.4%)	25 (10.6%)
Uncomplicated RIE	6 (5.0%)	4 (3.5%)	10 (4.3%)
Complicated bacteraemia	60 (50.0%)	61 (53.0%)	121 (51.5%)
Uncomplicated bacteraemia	32 (26.7%)	29 (25.2%)	61 (26.0%)
Left-sided IE	9 (7.5%)	9 (7.8%)	18 (7.7%)

* vancomycin or a semi-synthetic penicillin (oxacillin, cloxacillin, nafcillin, flucloxacillin) **± gentamicin**

Only 19 of the 120 patients treated with CUBICIN (16/115 in the comparator group) met the criteria for right-sided IE. Of these 19 patients, 11 were infected with methicillin-sensitive *Staphylococcus aureus* and 8 with MRSA.
Following a CHMP request , patients were classified according to whether or not a focus of infection was identified at baseline (microbiological infection site): 63.8% (150/235) of patients had bacteraemia with no documented associated focus of infection [65% (78/120) in the CUBICIN group and 62.2% (72/115) in the comparator group].
The median duration of treatment was 14 days in the CUBICIN group and 15 days in the comparator group. Treatment was administered in combination with gentamicin during the initial treatment period in 107/115 patients (93%) for the comparator group and 1 patient (0.8%) for the CUBICIN group, with a median treatment duration of 4 days.

- **Clinical response following treatment**

Table 3: Clinical success, evaluated during the TOC visit

Clinical success	CUBICIN	Comparator	95% CI *
Intention-to-treat population (ITT)			
All patients	53/120 (44.2)	48/115 (41.7)	2.4 [-10.2; 15.1]
Patients with IE	41/90 (45.6)	37/91 (40.7)	4.9 (-9.5; 19.3)
Definite IE	7/17	8/20	
Possible IE	34/73 (46.6)	29/71 (40.8)	5.7 (-10.4;21.9)
Per-Protocol Population (PP)			
All patients	43/79 (54.4)	32/60 (53.3)	1.1 [-15.6; 17.8]
Patients with IE	32/62 (51.6)	24/44 (54.5)	-2.9 (-22.2; 16.3)
Definite IE	5/13	5/11	
Possible IE	27/49 (55.1)	19/33 (57.6)	-2.5 (-24.3;19.4)

* confidence interval of difference (CUBICIN – comparator)

Table 4: Clinical success evaluated during the TOC visit, breakdown by diagnosis made by the independent experts committee

Clinical success	CUBICIN	Comparator
RIE		
ITT Population	8/19	7/16
Per-Protocol Population (PP)	6/12	4/8
Focus of infection identified at baseline		
Focus of infection not documented	34/78 (43.6 %)	31/72 (43.1%)
Catheter	9/16	5/10
Skin/wound infection	5/17	7/14
Other	5/9	5/9

At TOC, results for all patients (whatever the diagnosis) suggested that CUBICIN was non-inferior to the comparator treatment in the PP and ITT populations (the non-inferiority threshold was defined in advance: lower limit of the confidence interval of the difference > - 20%).
However, in the sub-group of patients with IE (definite or possible), the lower limit of the confidence interval of the difference between the two treatment groups in the PP population was lower than the previously stated non-inferiority threshold (difference -2.9%; 95% CI [-22.2 – 16.3]). That means that CUBICIN cannot be stated as non-inferior to the comparator treatment in the treatment of IE.
In addition, the results of this study don't permit to conclude onthe efficacy of CUBICIN in the treatment of bacteraemia, whatever the focus of infection, due to the small number of patients with a documented focus of infection at baseline.

Treatment failure
The overall failure rate was comparable in the two treatment groups (55.8% vs 58.3%).
Treatment failure caused by persistent or recurrent SAB infection was observed in 19/120 (15.8%) patients treated with CUBICIN and 11/115 (9.6 %) patients in the comparator group [including 9/53 (16.7%) patients treated with vancomycin and 2/62 (3.2%) patients treated with an anti-staphylococcus semi-synthetic penicillin].
Of these failures, 6 patients treated with CUBICIN and 1 treated with vancomycin were infected with SAB for which MIC of daptomycin increased during or after treatment.

3.2. Safety

The incidence of adverse events was comparable in the two treatment groups (95.8% in the CUBICIN group compared with 94.8% in the comparator group). The incidence of adverse effects was 35% in patients treated with CUBICIN and 42.2% in those treated with the comparator.

The most frequently reported adverse effects were: diarrhoea (1.7% in the CUBICIN group *versus* 9.5% in the comparator group), increased serum CPK (5% *versus* 0%), nausea (1.7% compared with 5.2%) and renal failure (1.7% *versus* 6%).
treatment was stopped because of adverse effects in 8.3% of patients treated with CUBICIN, (3 cases of increased serum CPK, 3 cases of rash, 1 case of vomiting, 1 case of renal failure, 1 case of thrombocytopenia and 1 cardiac arrest) and in 11.2% of patients treated withthe comparator therapy (rash and hypersensitivity reaction in 7 patients, 4 cases of renal failure and 2 of pyrexia).
Increased CPK > 500 IU/L associated with clinical muscular signs or asthenia was observed in 2.6% (3/116) of subjects in the CUBICIN group (and 0 in the comparator group); in 2 of these patients the increased CPK could been explained by an other aetiology than CUBICIN (statin treatment in one case, and muscle trauma in the other). Recommendations for CPK monitoring were included in the SPC.

Overall, the safety profile of CUBICIN, as observed in this new study, is in line with the effects expected and observed in previous studies (see SPC: clinical experience).

3.3. Conclusion

Clinical data on the efficacy of CUBICIN in the treatment of RIE caused by Staphylococcus aureus are from a controlled open-label study (the DAP-IE-01-02 study), where the objective was to demonstrate the non-inferiority of this treatment in comparison to “conventional" treatment [semi-synthetic penicillin or vancomycin ± gentamicin] in the treatment of bacteraemia or IE involving SAB.

Only 19 of the 120 patients treated with CUBICIN met the RIE criteria . Of these 19 patients, 11 had infection with methicillin-sensitive SAB and 8 had infection with MRSA.
Treatment response (clinical success) was observed in 8/19 patients in the CUBICIN group and 7/16 patients in the comparator group. These limited data do not permit to certainty conclude on the efficacy and safety of this product in the treatment of RIE caused by SAB, particularly in comparison to “conventional” treatment (semi-synthetic penicillin or vancomycin ± gentamicin or other antistaphylococcus agent).

The efficacy of CUBICIN in patients with infection of a prosthetic valve (an exclusion criterion) or left-sided IE caused by SAB was not demonstrated.
In addition, the results of this study on the bacteraemia treatment must be interpreted with caution, as only a very small number of well documented patients were included[3]. As a consequence, no certain conclusions can be drawn on the basis of this study for the efficacy of CUBICIN in the treatment of bacteraemia, whatever the initial infection location .

The safety profile of CUBICIN, as observed in this new study, is in line with the effects expected and observed in previous studies (see SPC: clinical experience).

[3] The choice of drug or combination therapy is guided by the location of the initial infection and the isolate. *Le Popi, CMIT, 2007, 9th edition: 15-17*

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

IE is a serious condition that can be life-threatening in itself or because of its complications (heart failure, ischaemia caused by embolism or haemorrhage, arrhythmias and conduction disorders etc). IE involving staphylococcus and IE involving prostheses are associated with the highest mortality rates. IE of the right heart must be considered patient by patient, as anatomical area, clinical picture and management differ from those found in left-sided endocarditis. Despite a significant risk of embolism, RIE is the most often medically treated and has a relatively good prognosis, especially depending on the patient's history (underlying neoplasia) and the risk of recurrence (drug abuse).

These products are curative treatments for RIE caused by SAB.

Clinical data on the efficacy and safety of CUBICIN in the treatment of RIE caused by SAB are very limited. The efficacy of CUBICIN in patients with infection of a prosthetic valve or left-sided IE caused by SAB was not demonstrated.

There are therapeutic alternatives, including for treatment of multiresistant organisms.

Public health benefit

The public health burden of patients with these indications is small, given the small numbers of patients.

Making new agents available to combat the spread of pathogenic bacteria with acquired resistance to antibiotics is a public health need.

However, given the available data, CUBICIN is not expected to have an additional impact on morbidity and mortality in comparison to therapies used in current clinical practice.

CUBICIN therefore does not provide an additional response to the identified public health need.

Consequently, CUBICIN is not expected to benefit public health in these indications.

The actual benefit of this medicinal product is moderate.

4.2. Improvement in actual benefit

Given the current data, CUBICIN does not provide an improvement in actual benefit (IAB V) in comparison to therapies used in current clinical practice to treat RIE caused by SAB and SAB associated with RIE or cSSTI.

It is a supplementary therapy, and its role in therapeutic strategy needs to be clarified.

4.3. Therapeutic use

Antibiotic treatment depend on identified or likely bacteria involved and on their levels of resistance, and must be bactericidal. In IE involving SAB, the therapeutic regimen varies depending on the IE involvement of a native or a prosthetic valve, and requires semi-synthetic penicillins resistant to penicillinase. In cases of MRSA, vancomycin is usually used. It is customary to treat IE with a combination of antibiotics (see table 5).

Table 5: Therapeutic options for Staphylococcus endocarditis (from E Pilly 2006)

Clinical situation	Bacterium	No penicillin allergy		Penicillin allergy		Duration
		Product	Dose	Product	Dose	
Native valve	***Methicillin-sensitive Staphylococcus***	Oxacillin[3] + Gentamicin[2]	150 mg/kg/day 3 mg/kg/day	Vancomycin[4] or cefamandole[6] + gentamicin[2]	30 mg/kg/day 75-100 mg/kg/day 3 mg/kg/day	4-6 weeks (5 days of combination)
	Methicillin-resistant Staphylococcus	Vancomycin[4] ± gentamicin or other antistaphylococcus agent, depending on sensitivity	30 mg/kg/day 3 mg/kg/day	Vancomycin[4] ± gentamicin or other antistaphylococcus agent, depending on sensitivity	30 mg/kg/day 3 mg/kg/day	4-6 weeks (gentamicin limited to 5 days)
Prosthetic valve[1]	***Methicillin-sensitive Staphylococcus***	Oxacillin[3] + gentamicin[2] ± rifampicin	150 mg/kg/day 3 mg/kg/day 20-30 mg/kg/day	Vancomycin[4] + gentamicin[2] + rifampicin	30 mg/kg/day 3 mg/kg/day 20-30 mg/kg/day	4-6 weeks (aminoside limited to 15 days)
	Methicillin-R, gentamicin-S Staphylococcus	Vancomycin[4] + gentamicin + rifampicin, or other antistaphylococcus agent, depending on sensitivity	30 mg/kg/day 3 mg/kg/day 20-30 mg/kg/day	Vancomycin[4] + gentamicin + rifampicin, or other antistaphylococcus agent, depending on sensitivity	30 mg/kg/day 3 mg/kg/day 20-30 mg/kg/day	4-6 weeks of combination treatment (aminoside limited to 15 days)
	Methicillin-R, gentamicin-R Staphylococcus	Vancomycin[4] + rifampicin[5] + other antistaphylococcus agent, depending on sensitivity	30 mg/kg/day 20-30 mg/kg/day	Vancomycin[4] + rifampicin[5] + other antistaphylococcus agent, depending on sensitivity	30 mg/kg/day 20-30 mg/kg/day	4-6 weeks of triple combination

[1] surgery considered as practically indispensable
[2] Alternatives: netilmicin (5-6 mg/kg/day)
[3] Alternatives: cloxacillin 100-150 mg/kg/day; cefamandole 75-100 mg/kg/day
[4] Alternatives: teicoplanin, with residual serum levels to be maintained between 20 and 30 mg/L
[5] If the strain is resistant to rifampicin, combination treatment with vancomycin and one or two other antibiotics should be considered, depending on data from sensitivity testing
[6] Use of a cephalosporin is not recommended in patients who have immediate-type penicillin allergy.

- Role of CUBICIN

It is currently difficult to state the precise role of CUBICIN, as there is insufficient data about its clinical efficacy.
For the indications of the MA, CUBICIN would be mainly reserved to patients requiring intravenous treatment for infection with multiresistant bacteria (MRSA) sensitive to daptomycin, and particularly when there is no therapeutic alternative.

4.4. Target Population

The incidence of IE in France seems to be stable. The standardised annual incidence in 1999 was 30 cases per year per million inhabitants[4], giving 1900 cases per year[5]. Around 23% of cases are caused by *SAB*[11], or 437 cases per year.

[4] Hoen B, Alla F, Selton-Suty C *et al*. Changing profile of infective endocarditis. Results of a 1-year survey in France. JAMA, 2002, 288: 75 – 81.

IE affecting solely the right heart represents 5-10% of the total cases of IE[6], or around 20-45 cases per year.
In practice, the number of patients likely to receive CUBICIN is smaller, given the low percentage of patients who would be particularly suitable for this treatment (clinical forms involving multi-resistant organisms sensitive to daptomycin, and particularly where there is no therapeutic alternative).

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the new indication and at the dosage in the Marketing Authorisation.

[5] Estimated using the 2007 demographic survey (N = 63,392,100). Insee Première n°1170 – January 2008
[6] J-P Delahaye and C Leport. Endocardites Infectieuses [Infective Endocarditis]. In: Pierre Godeau: Traité de Médecine. Paris, Flammarion, Médecine-Sciences, 2004: 1746-1754.