HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

18 October 2006

CUBICIN 350 mg (daptomycin), powder for perfusion solution
Box of 1 bottle (CIP code: 567 219-3)
CUBICIN 500 mg (daptomycin), powder for perfusion solution
Box of 1 bottle (CIP code: 567 220-1)

Applicant : NOVARTIS PHARMA S.A.S Laboratories

daptomycin

List I
Medicine for hospital prescription only.

Date of Marketing Authorisation (M/A): 19 January 2006

European Marketing Authorisation : subject to centralised procedure

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use in hospitals

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Daptomycin

1.2. Background

Cubicin is the first representative of a new class of antibacterials: cyclic lipopeptides.

1.3. Indication

Cubicin is indicated in the treatment of complicated infections of the skin and soft tissues in adults.

Daptomycin is only effective against Gram-positive bacteria.

In the case of mixed polymicrobial infections which may involve Gram-negative bacteria and/or some types of anaerobic bacteria, Cubicin must be associated with one or more suitable antibiotics.

The French recommendations regarding appropriate use of antibacterials should be taken into account.

1.4. Dosage

The recommended dose in adults is 4 mg/kg administered once every 24 hours, for 7 to 14 days or until the infection is terminated.

Kidney failure:
Daptomycin is mainly eliminated through the kidneys.

- *Patients with a creatinine clearance of ≥ 30 ml/min*

No dose adjustment is required in patients with a creatinine clearance of ≥ 30 ml/min. However, due to the limited clinical experience with the drug, the treatment response to the and the kidney function must be closely monitored in all patients who have already suffered from kidney failure (creatinine clearance < 80 ml/min).

- *Patients with a creatinine clearance < 30 ml/min*

The choice of interval between doses indicated hereafter has not been subnmitted to clinical evaluation in terms of either safety or efficacy; it is based on a pharmacokinetic data model. Thus Cubicin must only be used in patients in whom the clinical benefit prevails over the potential risks. The clinical response to the treatment and the kidney function must be closely monitored.

The dose must be reduced to 4 mg/kg administered in a single dose every 48 hours in patients with a creatinine clearance of < 30 ml/min who are treated by haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). If possible, Cubicin should be administered after dialysis on dialysis days.

Liver failure
No dose adjustment is required in the case of mild to moderate liver failure (Child-Pugh score B). No data are available for patients with severe liver failure (Child-Pugh score C). Cautions must therefore be taken when Cubicin is administered to these patients.

Elderly patients
The recommended dose (4 mg/kg once a day) is the same, except for patients with severe kidney failure. However, as data related to safety and efficacy of daptomycin in patients over 65 years old are limited, cautions should be taken if Cubicin is administered to them.

Children and adolescents (< 18 years)
There is no data related to the safety and efficacy of Cubicin in children and adolescents; its use is not recommended in patients under age 18.

Method of administration
Cubicin is administered via intravenous perfusion over a period of 30 minutes.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification

J : General anti-infectives for systemic use
01 : Antibacterials for systemic use
XX09 : Antibacterials for general use and other antibacterials

2.2. Medicines in the same therapeutic category

Not applicable

2.3. Medicines with a similar therapeutic aim

Medicinal products with the same therapeutic purpose are those which have the same indications; especially : beta-lactams, quinolones, macrolides, glycopeptides, aminoglycosides, oxazolidinones and synergistins.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

3.1.1. Characteristics of studies

The clinical development programme for Cubicin includes two pivotal non-inferiority studies (DAP - SST - 98-01 and DAP - SST - 99-01). Their main objectives were to demonstrate non inferiority of Cubicin (4mg/kg/day) compared to a standard treatment[1] in the treatment of complicated infections of the skin and soft tissues secondary to Gram-positive bacteria. Cubicin was to be considered not inferior to the comparator treatment if, for a 95% confidence interval, the difference between the clinical success rate of the comparator treatment and Cubicin was less than 10%.

Inclusion criteria:

- patients aged 18 to 85 years
- patients with a complicated[2] proven or suspected Gram-positive infection of the skin or soft tissues requiring hospitalisation
- patients who presented at least 3 of the following signs and symptoms: fever, white blood cell level > 12,000/mm^3 or a variation of ≥ ±10% from the normal value, pain, sensitivity to palpation, rash (extension of at least 1cm around the edges of the sore), oedema, hardening, pus formation
- patients with a complicated infection of the skin or soft tissues, the severity of which required hospitalisation and an antibacterial treatment lasting at least 4 days (study 99-01).

Patients suffering from bacteraemia were not to be included.

[1] Semi-synthetic penicillins are the standard treatment for infections of the skin and soft tissues. Vancomycin is used in patients with Methicillin-Resistant Staphylococcus Aureus.
[2] Complication criteria (according to the FDA): an infection of the deep soft tissues or an infection requiring surgery, existing skin lesions, and all underlying disorders whose effects may affect the release of the drug in the lesion, induce an immune response or prevent healing.

Treatments:

The eligible patients were randomised, after stratification based on the presence or absence of a diabetic ulcer, to receive:

- either Cubicin: 4 mg/kg once a day by i.v., for 7-14 days,
- or the comparator treatment: vancomycin, 1 g i.v. every 12 hours, or semi-synthetic penicillin (oxacillin, cloxacillin, nafcillin or flucloxacillin) 4 to 12 g/day i.v., for 7-14 days.

In the case of a polymicrobial infection which was proved or suspected to be caused by Gram-negative or anaerobic bacteria, the said treatments could be associated with aztreonam and/or metronidazole.

Primary efficacy endpoint:

The primary efficacy endpoint was the clinical response (clinical success or failure), assessed 7 to 12 days after the end of the treatment in the modified intention-to-treat population (m-ITT)[3] or in the Clinically Evaluable population (CE)[4]. Clinical success was defined as: patients who had been treated for at least 4 days and were judged by the investigator to have been cured ("clinically significant resolution of the clinical signs and symptoms due to the skin infection") or to have improved ("partial resolution of the signs and symptoms associated with the skin infection, so that another antibiotic treatment was unnecessary") 7 to 12 days after the treatment.

3.1.2. Results of studies

- **Study population**

	Study 98-01		**Study 99-01**	
	Cubicin	**Comparator***	**Cubicin**	**Comparator***
Randomised no.	272	275	277	294
Randomised untreated	8	9	7	2
Intention-to-treat population (ITT) no. (%)	256	261	270	292
Modified intention-to-treat population (MITT) no. (%)[a]	209 (81.6)	212 (81.2)	213 (78.9)	255 (87.3)
Clinically evaluable population (CE) no. (%)	223 (87.1)	222 (85.1)	245 (90.7)	262 (89.7)
Microbiologically evaluable (ME)[5]	187 (73.0)	189 (72.4)	196 (72.6)	231 (79.1)

[a] percentage calculated on the basis of the ITT population

*** vancomycin or semi-synthetic penicillin**

At inclusion, the demographic and medical characteristics of the patients were similar between the two treatment groups in the two studies. The mean age of the patients included was 52 years (55% male). 27% of the patients were over 65 years old. The most frequent infections in the patients treated with Cubicin were infected sores (42%), followed by abscesses (26%), infected diabetic ulcers (11%) and non-diabetic ulcers (13%). General signs of infection were observed in less than half of the patients (36% of patients met the SIRS criteria[6]). The main co-morbidity factors were diabetes (30%) and peripheral vascular disease (19%). 3% of patients suffered from immune deficiency, and 3% from bacteraemia. The bacteria most often isolated

[3] m-ITT: all patients included in the ITT population who presented an infection caused by Gram-positive bacteria which was documented on inclusion.

[4] CE: all patients included in the ITT population who met the inclusion and non-inclusion criteria defined by the protocol.

[5] ME: the microbiologically evaluable population (ME): the clinically evaluable population presenting a documented infection caused by Gram-positive bacteria on inclusion.

[6] SIRS is defined as: Temperature > 38°C or < 36 °C, heart rate > 90 beats per minute, breathing rate > 20 breaths per minute, white blood cells = 12,000/mm^3, or < 4,000/mm^3 or > 10% compared with the normal value.

were *Staphylococcus aureus* (71.3% of patients, 9.3% of whom had *Met-R Staphylococcus*), followed by *Streptococcus pyogenes* (21.5%), *Streptococcus agalactiae* (7%) and *Enterococcus faecalis* (10.5%).

- **Clinical response after treatment**

Clinical success rate (m – m ITT population)

	Study 98-01			Study 99-01		
	Cubicin	**Comparator***	**95% CI ****	**Cubicin**	**Comparator***	**95% CI****
Modified intention-to-treat population (m-ITT)						
	n = 209	**n =212**		**n = 213**	**n = 255**	
Clinical success	140 (67%)	142 (67%)	**[-9.0 ; 9.0]**	180 (84.5)	214 (83.9)	**[-7.2 ; 6.0]**
Cure	91 (44%)	85 (40%)		82 (38.5)	110 (43.1)	
Improvement	49 (23%)	57 (27%)		98 (46 %)	104 (40,8%)	
Clinical failure	69 (33%)	70 (33%)		33 (15.5)	41 (16.1)	
Clinically evaluatable population (CE)						
	n = 223	**n =222**		**n = 238**	**n =250**	
Clinical success	167 (75%)	166 (75%)	**[-8.2 ; 8.0]**	217 (88.6%)	235 (89.7%)	**[-4.3 ; 6.5]**
Cure	110 (49 %)	100 (45%)		103 (42%)	122 (46.6%)	
Improvement	57 (26%)	66 (30%)		114 (46.5%)	113 (43.1%)	
Clinical failure	56 (25%)	56 (25%)		28 (11.4%)	27 (10.3%)	

***** vancomycin or semi-synthetic penicillin
** confidence interval of the difference (comparator - Cubicin)

Clinical success rate on the basis of the pathogenic agent

	Study 98-01			Study 99-01		
	Cubicin	**Comparator***	**95% CI****	**Cubicin**	**Comparator***	**95% CI ****
S. aureus	100/150 (67)	96/147 (65)	[-12.1 ; 9.4]	123/149 (82.6)	145/173 (83.8)	[-6.9 ; 9.5]
S. aureus (SASM)	73/103 (71)	66/97 (68)	[-15.6 ; 9.9]	ND	ND	
S. aureus (MRSA)	17/34 (50)	18/35 (51)	[-22.2 ; 25]	ND	ND	
S. pyogenes	27/33 (82)	25/35 (71)	ND	54/59 (91.5)	57/68 (83.8)	[-19 ; 3.6]
S. agalactiae	13/17	14/21	ND	11/13	9/18	
E. faecalis	13/25	19/33	ND	14/20	23/28	

*vancomycin or semi-synthetic penicillin
** confidence interval of the difference (comparator - Cubicin)

- **Microbiological response (ME population)**

In study 98-01, the microbiological eradication rate (eradication assumed after clinical success) was 87.9% in the Cubicin group and 86.6% in the comparator group. In study 99-01, the eradication rate was 80% in the Cubicin group and 82% in the comparator group.

3.2. Undesirable effects

1474 subjects received Cubicin during the clinical trials, 800 of whom were given a 7-14 day treatment at a therapeutic dose. Adverse effects, considered to be at least possibly linked to the treatment, were reported in 20% of the patients treated with Cubicin and 19% of the subjects who received a comparator treatment. The treatment was discontinued early due to the onset of adverse effects in 5% of the patients treated with Cubicin and 3% of the subjects treated with comparator treatment.

The most frequently reported adverse effects during the treatment with Cubicin and until 14 days after its termination were headache, nausea, vomiting, diarrhoea, muscle pain, fungal infections, rash, reaction at the perfusion site, increased Creatine phosphokinase (CPK) and liver enzymes: alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase. Recommendations for CPK monitoring are included in the SPC.
Musculoskeletal disorders (myositis, muscle weakness, muscle pain and joint pain) were infrequent (< 0.01%).

3.3. Conclusion

The two non-inferiority clinical trials (studies 98-01 and 99-01) evaluated the clinical efficacy of daptomycin (Cubicin) in the treatment of complicated[7] proven or suspected infections of the skin and soft tissues caused by Gram-positive bacteria. They showed the non-inferiority (at the delta threshold=10%) of Cubicin (4 mg/kg once a day i.v.) compared with vancomycin or a semi-synthetic penicillin (nafcillin, cloxacillin, flucloxacillin or oxacillin). The clinical success rate of Cubicin (cure and clinical improvement in the m-ITT population) was 67% (95% CI[8] -9.0; 9.0) in study 98-01 and 84% (95% CI: -7.2; 6.0) in study 99-01.

However, the clinical significance of these results is debatable. The population studied basically comprises infected sores (42%), abscesses (26%), diabetic ulcers (11%) and non-diabetic ulcers (13%), but no patients with bacteraemia or severe skin infections such as bacterial dermohypodermitis (e.g. cellulitis or necrotising fascitis), suspected to be caused by Methicillin-resistant Staphylococcus aureus (MRSA), and very few patients suffering from severe underlying disorders (3% of patients with immune deficiency). Moreover, general signs of infection were observed in less than half the patients (36% of the patients who met the SIRS criteria[9]). The clinical efficacy of daptomycin against *Enterococcus faecalis* and *Enterococcus faecium* has not been established.

Consequently, the available data do not allow this medicinal product to be positioned adequately in the therapeutic management of severe infections and/or those due to resistant bacteria, compared with regularly effective molecules such as penicillinase-resistant beta-lactams.

The adverse effects most frequently associated with daptomycin were headache, nausea, vomiting, diarrhoea, muscle pain, fungal infections, rash, reaction at the perfusion site,
increased Creatine phosphokinase (CPK) and liver enzymes: alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatise. Recommandations for CPK monitoring are included in the SPC.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit (AB)

The disorders treated by these drugs can be life-threatening to the patient, either immediately or as a result of complications.

These drugs are classed as curative treatments.

The efficacy/safety ratio of these medicinal products is high in forms of low or moderate severity. In severe forms, the efficacy/safety ratio remains to be evaluated.

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[7] defined according to the FDA criteria: an infection of the deep soft tissues or an infection requiring surgery, existing skin lesions, all underlying disorders whose effects may affect the release of the drug in the lesion, induce an immune response or prevent healing.

[8] Confidence interval of the difference (Comparator - CUBICIN)

[9] SIRS is defined as: Temperature > 38°C or < 36 °C, heart rate > 90 beats per minute, breathing rate > 20 breaths per minute, white blood cells = 12,000/mm^3, or < 4,000/mm^3 or > 10% compared with the normal value.

There are alternative treatments, including treatments for multiresistant germs.

Public health benefit

In view of the small number of patients likely to be concerned, the public health burden of complicated infections of the skin and soft tissues in the population of patients eligible for treatment with Cubicin is low.

Obtaining new molecules to deal with the spread of pathogenic bacteria which have acquired resistance mechanisms to antibiotics constitutes a public health need.

In infections of low or moderate severity, no additional impact on the reduction of morbidity is expected, compared with the treatments used in current practice.

In severe infections and/or those caused by resistant bacteria, the available data are insufficient to assess the expected impact of Cubicin reducing morbidity.

The transferability of the experimental data is not guaranteed, as the patients included in the trials were not representative of those likely to receive Cubicin in practice. The response to the public health need has therefore not been established according to the current state of the art.

No public health benefit is therefore expected from Cubicin.

However, the AB of Cubicin is substantial.

4.2. Improvement in actual benefit (IAB)

According to the available data, it has not been demonstrated that Cubicin provides an improvement in actual benefit compared with the treatments used in the current management of complicated infections of the skin and soft tissues (IAB V).

However, it constitutes an additional treatment for the management of those infections.

4.3. Therapeutic use

The usual treatment generally involves antibiotics suitable for the identified or likely bacteria. There are numerous possible choices, depending on the bacteria and their level of resistance. It is currently difficult to identify the place of Cubicin in view of the insufficient documentation on its clinical efficacy in severe infections and/or those due to multi-resistant bacteria.

In the indications stated in the Marketing Authorisation M/A, Cubicin should be reserved for patients requiring intravenous treatment, in the case of infections caused by multi-resistant bacteria sensitive to daptomycin for which no alternative treatment is available.

4.4. Target population

The indications for Cubicin are complicated infections of the skin and soft tissues treated on a hospital in-patient basis.

The target population of Cubicin is currently difficult to identify, as the clinical efficacy documentation is insufficient.

In practice, the number of patients liable to receive Cubicin is probably very small in view of the very low percentage of patients eligible for this treatment (complicated clinical forms with multi-resistant germs which are sensitive to daptomycin and for which there is no alternative treatment).

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the marketing authorisation condition.