TRANСПАРЕНЦИЯ КОМИССИИ

ОПИНИЯ

15 Октябрь 2008

MERONEM 1 г, порошок для раствора для IV инъекций
Пакет из 10 ампул (CIP: 387 830-6)

Источник: ASTRAZENECA

Меропеним

ATC Код: J01DH02

Список I
Медицина для применения в стационаре.

Дата маркетингового разрешения (национальный порядок): 16 апреля 1997 года, изменение от 18 февраля 2008 года

Фирменный препарат включён в список медикаментов, утвержденных для использования в стационарах и различных общественных службах.

Причина запроса: Включение в список медикаментов, финансирование Национального страхования и одобрение медицинскими учреждениями в расширении показания: "Лечение бронхиальных инфекций, вызванных Pseudomonas aeruginosa и/или Burkholderia cepacia, сопровождающихся цистической фиброзом".

Medical and Economic Evaluation and Public Health Division
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Meropenem

1.2. Background
Meropenem is a beta-lactam antibiotic belonging to the carbapenem class.

1.3. Indications (Including the extension of indication in bold type)
“These derive from the antibacterial activity and pharmacokinetic characteristics of meropenem. They take into account both the clinical studies conducted on this medicinal product and its place in the range of currently available antibacterial products. They are restricted to severe infections, with or without bacteraemia, caused by microorganisms susceptible to meropenem in the following indications:

*In adults:
- Lower respiratory tract infections,
- Abdominal infections,
- Febrile episodes in neutropenic patients.
- **Treatment of bronchopulmonary infections caused by Pseudomonas aeruginosa and/or Burkholderia cepacia associated with cystic fibrosis.**

*In children:
- Febrile episodes in neutropenic patients.
- **Treatment of bronchopulmonary infections caused by Pseudomonas aeruginosa and/or Burkholderia cepacia associated with cystic fibrosis.**

Bitherapy is required to treat infections caused by *Pseudomonas aeruginosa* and/or *Burkholderia cepacia*; meropenem must therefore be combined with another antibiotic. Official recommendations about the appropriate use of antibiotics should be taken into account.”

1.4. Dosage

*Adults:
The maximum dose used should not exceed 6 g/day in 3 divided doses.

In adults with normal renal function:
- Community-acquired lower respiratory tract infections: 500 mg IV every 8 hours.
- Nosocomial lower respiratory tract infections, abdominal infections, febrile episodes in neutropenic patients: 1 g IV every 8 hours.
- **Bronchopulmonary infections caused by Pseudomonas aeruginosa and/or Burkholderia cepacia associated with cystic fibrosis**: 2 g every 8 hours. The usual duration of treatment is 15 days.
In adults with renal insufficiency:
Relative to the defined unit dose (500 mg, 1 g) and administered every 8 hours, the dosage must be adjusted in patients with a creatinine clearance of \( \leq 50 \text{ ml/min} \), according to the following regimen:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Dosage (&quot;dose units&quot;: 500 mg or 1 g every 8 hours)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>26-50</td>
<td>1 dose unit</td>
<td>every 12 hours.</td>
</tr>
<tr>
<td>10-25</td>
<td>1/2 dose unit</td>
<td>every 12 hours.</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>1/2 dose unit</td>
<td>every 24 hours.</td>
</tr>
</tbody>
</table>

Meropenem is eliminated by haemodialysis; if continuous meropenem treatment is necessary, the administration of an additional dosage unit is recommended after haemodialysis.

There is no clinical experience in the case of peritoneal dialysis and haemofiltration.

In adults with hepatic insufficiency:
No dosage adjustment is necessary in patients with impaired hepatic function.

**Elderly:**
The dosage should be adjusted according to renal status.

No dosage adjustment is therefore necessary in elderly subjects with normal renal function or with a creatinine clearance greater than 50 ml/min.

**Child:**
The adult dose may be used in children over 50 kg.

In children with normal renal function:
- Febrile episodes in neutropenic patients. 20 mg/kg IV every 8 hours.
- Bronchopulmonary infections caused by *Pseudomonas aeruginosa* and/or *Burkholderia cepacia* associated with cystic fibrosis. 40 mg/kg every 8 hours. The usual duration of treatment is 15 days.

In children with hepatic or renal insufficiency:
No clinical experience is available.

**Method of administration**
Meropenem may be administered intravenously either in a direct bolus dose by slow injection (approximately 5 minutes) or by infusion over 15 to 30 minutes (cf. 6.2 Incompatibilities and 6.4 Special precautions for storage).

For use by slow bolus injection, the injected solution is obtained by dissolving the powder in water for Injections (10 ml for 500 mg of meropenem). This gives a concentration of 50 mg/ml. The reconstituted solution is colourless or pale yellow.

In the case of administration by infusion, the solution may be prepared with compatible solvents (50 to 200 ml) (cf. 6.2 Incompatibilities and 6.4 Special precautions for storage).
2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

J : general anti-infective agent for systemic use
J01 : antibacterial agents for systemic use
J01D : other beta-lactam antibiotics
J01DH : carbapenems
J01DH02 : meropenem

2.2. Medicines in the same therapeutic category

2.2.1. Comparator drugs

<table>
<thead>
<tr>
<th>INN /Proprietary name</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem/cilastatin</td>
<td>The indications of the intravenous forms are restricted to severe infections caused by microorganisms susceptible to imipenem (other than meningitis) and in particular: abdominal, bronchopulmonary and gynaecological infections, septicaemia, genitourinary, bone, joint, skin and soft tissue infections, endocarditis.</td>
</tr>
<tr>
<td>- TIENAM 250 mg IV</td>
<td>- TIENAM 500 mg IV</td>
</tr>
<tr>
<td>(MA adult and child)</td>
<td></td>
</tr>
</tbody>
</table>

2.3. Medicines with a similar therapeutic aim

These are antibiotics with the same or similar spectrum of antimicrobial activity, administered by the IV, oral or inhaled routes, recommended for the treatment of bronchopulmonary infections caused by *Pseudomonas aeruginosa (PA)* associated with cystic fibrosis.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Marketing authorisation was granted on the basis of a bibliographical dossier, including in particular:

- two comparative studies versus ceftazidime, in monotherapy or bitherapy with tobramycin, in cystic fibrosis patients,
- follow-up data for patients treated within the framework of compassionate programs.

Only the clinical studies versus active comparators were taken into account and are described below.

- As bitherapy: Comparative study of meropenem versus ceftazidime, in combination with tobramycin IV (Study by Blumer et al. 2005)²:

In this study, 102 patients (age > 5 years) with acute pulmonary exacerbations caused by *P. aeruginosa* susceptible to the antibiotics studied, were randomised, after stratification according to disease severity (evaluated from the maximum expiratory volume in one second - FEV₁)³, to receive single blind: either meropenem in combination with tobramycin (n=50 patients, 50% < 16 years) or ceftazidime in combination with tobramycin (n=52, 38.5% < 16 years).

Patients (N=19) infected by *Bulbholderia cepacia* or by *P. aeruginosa* resistant to ceftazidime were included in a third arm and treated open-label by meropenem in combination with tobramycin IV.

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¹ Consensus conference (Société Française de Pédiatrie, with the participation of the ANAES). management of cystic fibrosis patients. Pneumologie et infectiologie, November 2002.


³ Criteria of severity: mild = FEV₁ > 70% of theoretical value, moderate = FEV₁ between 40 and 69%, severe = FEV₁ < 40%.
The dose of meropenem ranged from 40 mg/kg/8 hours up to 2 g IV and that of ceftazidime 50 mg/kg/8 hours. The dose of ceftazidime was lower than the currently recommended dose of 200 to 300 mg/kg/24 hours in the child. Tobramycin was administered at a sufficient dosage to maintain a plasma peak ≥ 8 µg/ml and a trough plasma concentration < 2 µg/ml. The mean duration of treatment was 13.5 days (meropenem) versus 14.1 days (ceftazidime).

The severity of the exacerbation for patients treated by meropenem was: mild (22%), moderate (42%) or severe (36%), with no difference with the patients treated by ceftazidime.

The **primary efficacy endpoint** was the percentage change in FEV₁ between baseline and the end of treatment (or after 14 days of treatment for patients continuing their treatment beyond 14 days). Patients with a relative increase in FEV₁ ≥ 15% compared to baseline were considered to be responders.

**Main results:**

- **Responder patients at the end of treatment:** 63.8% (30/47) in the meropenem/tobramycin group **versus** 58% (29/50) in the ceftazidime/tobramycin group (NS).
- In the group of patients infected by *Bulholderia cepacia* or by *P. aeruginosa* resistant to ceftazidime, 6/18 evaluable patients were responders at the end of treatment.
- Overall clinical response: no new exacerbation for a median of 176 days (meropenem) **versus** 207 days (ceftazidime) (NS);
- Reduction in bacterial load: mean reduction in bacterial count at the end of treatment: 3.6 log (meropenem) **versus** 3.5 log (ceftazidime) (NS); a few resistant isolates of *P. aeruginosa* were found after treatment in the same proportion in the two groups.

- **As monotherapy: Comparative study of meropenem versus ceftazidime (Byrne et al. 1995)**

In this open-label comparative study, 40 patients with acute pulmonary exacerbations caused by *P. aeruginosa* susceptible to the antibiotic studied were randomised (2:1) to either meropenem (n=27 patients aged from 4 to 28 years, mean age 15 years) administered at the dosage of 25 mg/kg/8 hours IV (125 mg to 1250 mg) or ceftazidime (n=13 patients aged from 6 to 33 years, mean age 16 years) at the dosage of 50 mg/kg/8 hours. The first dose of antibiotic was administered in the hospital, with continuation of treatment at home for certain patients. Antibiotics were administered in a short infusion or a bolus dose.

The severity of the clinical manifestations of patients (adults only), evaluated by the SHWACHMAN⁵, score was moderate or low (score: 57 - 75). Overall, 75 exacerbations mainly due to *Pseudomonas aeruginos*a were considered to be evaluable. The mean duration of treatment was 15 days in the two treatment groups.

The primary endpoint was the overall clinical response (improvement in respiratory status, weight gain, improvement in general status).

**Overall clinical response**

<table>
<thead>
<tr>
<th>Overall clinical response*</th>
<th>Meropenem N = 54 episodes</th>
<th>Ceftazidime N = 21 episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the end of treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Improvement</td>
<td>53/54</td>
<td>19/21</td>
</tr>
<tr>
<td>- No change/deterioration</td>
<td>1/54</td>
<td>2/21</td>
</tr>
<tr>
<td>At the end of follow-up (4-6 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Improvement</td>
<td>43/50</td>
<td>17/20</td>
</tr>
<tr>
<td>- No change/deterioration</td>
<td>1/50</td>
<td>1/20</td>
</tr>
<tr>
<td>- Relapse</td>
<td>6/50</td>
<td>2/20</td>
</tr>
</tbody>
</table>

*improvement in respiratory status, weight gain, improvement in general status

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5 Degree of severity and prognosis according to SHWACHMAN and KULCZYCKI Score: Excellent = 100 to 86, Good = 85 to 71, moderate = 70 to 56, poor = 55 to 41, severe ≤ 40 %.
This study only gives an indication because of the small number of included patients and the absence of appropriate statistical analysis. In addition, the dose of meropenem administered in this study (25 mg/kg/8 hours IV [125 mg at 1250 mg]) was lower than the currently recommended dose (2 g/8 hours in adults and 40 mg/kg/8 hours in the child) in combination with another antibiotic (cf. SPC); it is unreasonable to propose meropenem as monotherapy during an exacerbation caused by Pseudomonas aeruginosa.

3.2. Safety

Few data are available on the safety of meropenem used at “high” doses (2g/8h in adults and 40 mg/kg/8h in the child) for the treatment of bronchopulmonary infections due to *Pseudomonas aeruginosa* and/or *Burkholderia cepacia* associated with cystic fibrosis.

The safety data of the study by Blumer et al in which meropenem was used at high doses (40 mg/kg/8 hours with up to 2 g IV, corresponding to the MA dosages) in combination with tobramycin, did not reveal any unexpected adverse effects. The incidence of adverse effects was 38% (19/50) in the meropenem /tobramycin group *versus* 40.4% (21/52) in the ceftazidime /tobramycin group (NS). Treatment discontinuations due to adverse effects were uncommon (2 patients in each group).

The main adverse effects were as follows: increase in transaminases (SGOT 14% vs 9.6%, SGPT 12%), increase in alkaline phosphatases (8% vs 1.9%), diarrhoea (6% vs 1.9%), nausea (4%), rash (6%), pharyngitis (6% vs 1.9%), headaches (4 % vs 9.6 %).

**Clinical experience**

The reported clinical experience on the use of meropenem, in particular at the MA dosages during compassionate care programs, and the pharmacovigilance data, did not give rise to any major concerns about the safety of this antibiotic.

The main undesirable effects described in the SPC are similar to those of beta-lactam antibiotics in general (cf. SPC).

3.3. Conclusion

Although only limited clinical data are presented, they confirm the efficacy of meropenem in combination with an aminoglycoside (tobramycin) in the treatment of bronchopulmonary infections caused by *Pseudomonas aeruginosa* and/or *Burkholderia cepacia* associated with cystic fibrosis.

The reported clinical experience on the use of meropenem, in particular at the “high doses” recommended in cystic fibrosis patients, did not give rise to any major concerns about the safety of this antibiotic.

Generally, the evaluation of efficacy and safety in the studies submitted in the application did not show that meropenem is more effective or better tolerated than other treatment options and in particular, the other beta-lactam antibiotics used to treat *Pseudomonas aeruginosa* in combination with an aminoglycoside.

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4.1. Actual benefit

Chronic infections with *Pseudomonas aeruginosa* contribute to the development of progressive respiratory failure, which is the main cause of morbidity and mortality of cystic fibrosis patients. The aim of antibiotic therapy is to reduce the bacterial inoculum, to increase the interval between exacerbations and to delay the deterioration in respiratory function.

This proprietary product has a high efficacy/safety ratio.

There are alternative treatments.

**Public health benefit**

In terms of public health, although cystic fibrosis is at present, a serious and incurable illness, the burden of this disease is moderate because of its relatively low prevalence.

In the indication concerned, the burden is low taking into account the even smaller number of patients.

The therapeutic need is considered to be only partially covered as there is no known effective pharmacotherapy for bronchial obstruction in cystic fibrosis patients. There is therefore a public health need in particular for patients infected by microorganisms resistant to antibiotics (in particular *Pseudomonas*).

According to the data provided, MERONEM had no additional impact on morbidity and mortality or quality of life compared to existing therapies.

The transposability is acceptable.

Given our current knowledge, it is not possible to determine if the proprietary medicine MERONEM addresses an identified public health need.

Consequently, according to the available data, MERONEM is not expected to have an impact on public health.

The actual benefit of this proprietary drug is substantial.

4.2. Improvement in actual benefit

According to the bibliographic data presented in the application and the reported clinical experience on the efficacy and safety of this product in the treatment of bronchopulmonary infections due to *Pseudomonas aeruginosa* and/or *Balkholderia cepacia* associated with cystic fibrosis, the Committee considers that MERONEM provides a minor improvement in actual benefit (IAB IV) in current management, taking into account the progressive resistance profile of *Pseudomonas aeruginosa* to carbapenems.

4.3. Therapeutic use

7 The role of bronchopulmonary infection in the morbidity and mortality of cystic fibrosis is well established. However, the management of this bronchopulmonary involvement must be integrated in overall disease management.

Bacterial colonisation occurs very early on during the natural history of the disease. The first causal microorganisms are *Haemophilus influenzae* and *Staphylococcus aureus*.

Infection by *Pseudomonas aeruginosa* constitutes a turning point in the progression of respiratory disease. At adult age, approximately 70% of patients are carriers of this microorganism.

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The treatment of primary colonisation by *P. aeruginosa* requires a combination of bactericidal antibiotics by the IV route (beta-lactam antibiotic + aminoglycoside), followed or not by treatment with inhaled antibiotics. The combination or oral ciprofloxacin and colistin sprays has also been proposed.

During chronic *P. aeruginosa* infections, it is important to treat the episodes of superinfection, usually by bitherapy with an anti-*Pseudomonas aeruginosa* beta-lactam antibiotic and an aminoglycoside by the IV route. These antibiotics are chosen according to the most recent antibiotic susceptibility tests and prior therapeutic responses.

In the case of multidrug-resistant strains, triple-agent therapy combining oral ciprofloxacin with bitherapy may be used. IV colistin is also a possible choice in this situation.

The benefit of inhaled antibiotic therapy in a systematic treatment plan for chronic bronchial *P. aeruginosa* infection has been confirmed. This type of maintenance treatment is particularly effective as the antibiotics are directly delivered to the site of endobronchial infection and toxicity is decreased by minimising systemic absorption. Inhaled tobramycin or colistin are also used.

A course of IV antibiotics should be given after even only minor signs of worsening of clinical status or respiratory function.

Systematic quarterly IV courses of treatment are still useful for patients with poor adherence to inhaled treatment or patients who are better stabilised by repeated IV courses. It may be useful to give ciprofloxacin orally between courses.

**Therapeutic use of meropenem**

MERONEM is one of the main antibiotics recommended for the management of bronchopulmonary infection by *Pseudomonas aeruginosa* and/or *Burkholderia cepacia* in cystic fibrosis patients.

This drug, like a large number of beta-lactam antibiotics, is available for pharmacy sale in order to facilitate access to outpatients requiring prolonged and controlled antibiotic treatment after discharge from hospital; in addition hospital prescription guarantees the management of its use.

**4.4. Target Population**

In France, the population of patients with cystic fibrosis is estimated to be approximately 5000.

In 2003, the National Cystic Fibrosis Observatory (ONM) reported that 37% of patients under 18 years of age and 68% of adults are chronically colonised by *Pseudomonas aeruginosa*. *Burkholderia cepacia* was found in 2.2% of all patients who had a cytobacteriological examination of the sputum in 2005.

As MERONEM is used in adults and children, the target population is estimated to be not more than 2500 and 3000 patients/year.

**4.5. Transparency Committee recommendations**

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicinal products approved for use by hospitals and various public services in the extension of indication and dosages of the MA.

- **4.5.1. Packaging**: Appropriate for the prescription conditions
- **4.5.2. Reimbursement rate** 65%

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8 French cystic fibrosis registry. assessment of 2005 data by the French Cystic Fibrosis Observatory. 2007