SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Negaban 1 g, powder for solution for injection/infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of temocillin as temocillin sodium.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion.
Vial containing a white to pale yellow sterile solid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Negaban is indicated for the treatment of septicaemia, urinary tract infection and lower respiratory tract infection where susceptible gram-negative bacilli are suspected or confirmed.

In mixed infections where gram-positive or anaerobic bacteria are also liable to be implicated, co-administration with other appropriate antibacterial agents should be considered.

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

4.2. Posology and Method of Administration

Adults (including the elderly): The usual dosage is 1-2 g every 12 hours.

Children: Insufficient data are available to recommend an appropriate dosage regime.
Dosage in patients with impaired renal or hepatic functions (adults):
Temocillin is mainly excreted renally and unchanged. Excretion is reduced in renal impairment and half-life is increased according to the severity of renal failure. In moderate and severe renal failure, dose adjustments are necessary in accordance with the following regimen:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Dosage per administration</th>
<th>Interval between administrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 60</td>
<td>1 to 2 g</td>
<td>12 h</td>
</tr>
<tr>
<td>60 to 30</td>
<td>1 g</td>
<td>12 h</td>
</tr>
<tr>
<td>30 to 10</td>
<td>1 g</td>
<td>24 h</td>
</tr>
<tr>
<td>Less than 10</td>
<td>1 g or 500 mg</td>
<td>48 h or 24 h</td>
</tr>
</tbody>
</table>

In case of hemodialysis: as a rule, the i.m. route should be avoided, considering the patient’s treatment with heparin. I.V. injection of Negaban is recommended, using water for injection as solvent: 1 g (I.V.) every 48 hours, preferably at the end of the hemodialysis. In case of daily hemodialysis: 500 mg (I.V.) after each hemodialysis.

In case of continuous peritoneal dialysis in ambulatory patients: 1 g Negaban i.m. every 48 hours.

These data are based on studies where creatinine clearance was used to estimate the degree of renal impairment.

Limited experience in patients with impaired hepatic function has not indicated a need for a reduction in dosage.

Method of administration:
Negaban may be administered by intravenous injection, intermittent intravenous infusion or intramuscular injection.

*Intravenous solutions:* See also Section 6.6. Negaban solutions should be administered by slow injection into the vein (3-4 minutes) or as an intravenous infusion over a period of 30-40 minutes.

*Intramuscular injection:* Negaban may be given intramuscularly after reconstitution (see Section 6.6.). If pain is experienced at the site of i.m. injection, a sterile solution of lidocaine hydrochloride 0.5-1% may be used in place of Water for Injections.

### 4.3 Contraindications
The use of Negaban is contraindicated in patients with a history of allergic reactions to any of the penicillins or any other type of beta-lactam drug.

### 4.4 Special warnings and precautions for use
Serious and occasionally fatal anaphylactic reactions have been reported in patients receiving therapy with penicillins. If an allergic reaction occurs during therapy with Negaban, the drug must be discontinued.

Cross-allergy with cephalosporins is very common (about 10%).

In patients with kidney failure, the posology must be adapted to the degree of insufficiency, as recommended in Section 4.2. Posology and Method of Administration.

Bleeding manifestations have occurred in some patients receiving beta-lactam antibiotics. These reactions have sometimes been assessed with abnormalities of coagulation tests and are more likely to occur in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

As with any antibiotic, temocillin may be associated with induced pseudomembranous colitis, although animal studies have never shown any induction of Clostridium difficile infection. In case of severe, persistent diarrhoea, caution is recommended, Negaban must be discontinued and suitable therapy be initiated (e.g. oral metronidazole or oral vancomycin). Preparations which inhibit peristalsis are contra-indicated.

As with other antibiotics, the possibility of emergence of resistant organisms which might cause superinfections should be kept in mind, particularly during prolonged treatment. Microbiological follow-up may be required to detect any important superinfection. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

Periodic electrolyte determinations should be made in patients with low potassium reserves and the possibility of hypokalaemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics. Modest elevations of indices of liver function may be observed.

1 vial of Negaban 1g contains 5 mmol of sodium.

4.5 Interaction with other medicinal products and other forms of interaction
None known.

4.6 Pregnancy and lactation
Animal studies with Negaban have shown no teratogenic effects. There is no experience of Negaban in human pregnancy. Therefore, its use in pregnancy cannot be recommended. Trace quantities of penicillins can be detected in the
milk of lactating mothers. Therefore, mothers should not breastfeed their infants while receiving Negaban.

4.7 Effects on ability to drive and use machines
None known.

4.8 Undesirable effects

Undesirable effects are typical of the injectable penicillins: they may include diarrhoea, pain at the site of I.M. injection, occasionally rash, either urticarial or erythematous. Certain reactions such as fever, arthralgia or myalgia, sometimes develop more than 48 hours after the start of the treatment. In any case, discontinuance of treatment and recourse to another appropriate antibiotic therapy are essential.

In common with other β-lactam antibiotics, angioedema and anaphylaxis have been reported.

There is also a risk of phlebitis and thrombophlebitis with intravenous administration of β-lactam antibiotics, although to a lesser extent in the case of Negaban.

In patients suffering from renal failure, neurological disorders with convulsions have been reported following the I.V. injection of high doses of penicillin.

4.9 Overdose

There have been no reported cases of overdosage. Dosages of up to 8 g daily have been administered to volunteers without untoward effects.

Negaban may be removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: β-lactam antibacterials - penicillins (ATC: J01CA17)
The product is an injectable antibiotic active in vitro against many aerobic gram-negative bacteria, with the notable exception of *Pseudomonas aeruginosa* and *Acinetobacter spp*.

**Mechanism of action:**
β-lactam antibiotics act by inhibiting the synthesis of the **peptidoglycan** layer of bacterial cell walls. β-lactam antibiotics irreversibly bind to the active site of specific transeptidases and carboxypeptidases known as Penicillin Binding Proteins (PBP), preventing peptidoglycan production.

**Mechanism of resistance:**
Temocillin is stable to most types of β-lactamases, including most AmpC and Extended Spectrum β-Lactamases. The only suspected mechanisms of resistance to temocillin are outer membrane impermeabilisation or active efflux. β-lactamase producing Enterobacteriaceae resistant to 2nd or 3rd generation cephalosporins may be sensitive to Negaban.

**Breakpoints following the BSAC (British Society for Antimicrobial Chemotherapy) method for Enterobacteriaceae:**
Susceptible organisms: MIC ≤ 8 mg/L
Resistant organisms: MIC > 8 mg/L

**Uncomplicated urinary tract infections:**
Susceptible organisms: MIC ≤ 32 mg/L
Resistant organisms: MIC > 32 mg/L

**Commonly susceptible organisms:**
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Citrobacter spp.*
- *Proteus mirabilis* - *Proteus spp* (indole +) - *Morganella morganii*
- *Pasteurella multocida* - *Providencia stuartii*
- *Salmonella typhimurium* - *Yersinia enterocolitica*
- *Moraxella catarrhalis*
- *Haemophilus influenzae*
- *Neisseria meningitides*

**Species for which acquired resistance may be a problem:**
- *Serratia marcescens*
- Enterobacter spp.

Inherently resistant organisms:
- Acinetobacter spp.
- Pseudomonas aeruginosa
- Gram positive organisms
- Anaerobic bacteria

5.2 Pharmacokinetic properties

Mean pharmacokinetic parameters of temocillin following administration of a single dose:

<table>
<thead>
<tr>
<th>MEAN PARAMETER</th>
<th>HEALTHY SUBJECTS</th>
<th>ELDERLY PATIENTS</th>
<th>RENALLY IMPAIRED PATIENTS*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I.V. BOLUS</td>
<td>I.M.</td>
<td>I.V.</td>
</tr>
<tr>
<td>Dose</td>
<td>1 g</td>
<td>2 g</td>
<td>4 g</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>6</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>173.3</td>
<td>281.2</td>
<td>482.9</td>
</tr>
<tr>
<td>T½β (h)</td>
<td>4.2</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>CLtot (ml/min)</td>
<td>33.2</td>
<td>38.3</td>
<td>48.5</td>
</tr>
<tr>
<td>VDss (L)</td>
<td>11.1</td>
<td>12.1</td>
<td>14.7</td>
</tr>
</tbody>
</table>

* = Not determined
⁺ = CCR < 10 ml/min/1.73m²
⁺⁺ = Approx. 1 h post-dose

Distribution: The protein serum binding rate is 85% in healthy volunteers. Concentrations of temocillin in gall bladder bile at a mean of 2.4 hours after I.V. injection of 1 g were variable. Temocillin was not detected in the bile of 2 out of 10 patients but in some cases concentrations were considerably higher than those in serum. The mean concentration in gall bladder bile was 205 µg/ml. Concentrations of temocillin in prostate homogenate between 1 and 3 hours after I.M. injection of 1 g of temocillin ranged from 2.3-16 µg/ml (mean 8.25) compared with a mean serum concentration of 12.5 µg/ml.

In a series of studies, the penetration of temocillin into tissues was investigated by assaying either tissue fluid or homogenate for temocillin. Following I.V. injection of 1 g of temocillin, concentrations in the fluid of cantharidine-induced skin blisters reached a mean peak of 44.3 µg/ml at 3 hours. The mean half-life of temocillin in blister fluid was 4.0 hours. Temocillin concentrations in peripheral lymph after a 1 g I.V. injection were of a similar order to those in blister fluid, reaching a mean peak of 30.6 µg/ml between 1.5 and 2 hours. The mean half-life of elimination from lymph was
4.4 hours. As was found in skin blisters, concentrations of temocillin in lymph were above the MIC of susceptible bacteria at 12 hours after administration. Only a small proportion of temocillin passes into the cerebrospinal fluid.

**Excretion**: Temocillin is excreted unchanged mainly in the kidney. Excretion may be delayed in cases of kidney failure so the dosage must be reduced, depending on the degree of kidney failure shown by the creatinine clearance values.

**Pharmacokinetic parameters in renal impairment**:

<table>
<thead>
<tr>
<th>creatinin clearance (ml/min)</th>
<th>No. of subjects</th>
<th>Dose (g)</th>
<th>Cmax (mg/L)</th>
<th>T½β (h)</th>
<th>CLtot (ml/min)</th>
<th>VDss (L)</th>
<th>urine excretion (% in 24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-60</td>
<td>5</td>
<td>0.5</td>
<td>69.8</td>
<td>13.6</td>
<td>16.3</td>
<td>16.3</td>
<td>51.6</td>
</tr>
<tr>
<td>10-30</td>
<td>2</td>
<td>0.5</td>
<td>49.4</td>
<td>18.9</td>
<td>13.3</td>
<td>16.0</td>
<td>23.1</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>5</td>
<td>0.5</td>
<td>49.5</td>
<td>28.2</td>
<td>8.8</td>
<td>19.9</td>
<td>8.3</td>
</tr>
</tbody>
</table>

- = Not determined

5.3 **Preclinical safety data**

No information additional to that already contained in this Summary of Product Characteristics.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

None.

6.2 **Incompatibilities**

Negaban should not be mixed with the following in the syringe, intravenous fluid container or giving set:
- Proteinaceous fluids (e.g. protein hydrolysates)
- Blood products
- Intravenous lipid emulsions
- Aminoglycosides

This medicinal product must not be mixed with other products except those mentioned in section 6.6.
6.3 Shelf life

Dry powder: 3 years
Shelf life after reconstitution: see Section 6.6. Special precautions for disposal and other handling.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Store in the original package.

6.5 Nature and contents of container

Clear glass vials 15 ml, 25 ml and 50 ml with butyl rubber stoppers and either aluminium seal or aluminium plastic seal in packs of 1 vial or 5 vials.

6.6 Special precautions for disposal and other handling

Negaban is not intended for multi-dose use, any part-used antibiotic solution should be discarded. Solutions are normally a pale yellow colour.

**Intravenous injection**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Recommended volume of Water for Injections BP to be added for dissolution</th>
<th>Final volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g</td>
<td>10 ml</td>
<td>10.7 ml</td>
</tr>
<tr>
<td>2 g</td>
<td>20 ml</td>
<td>21.4 ml</td>
</tr>
</tbody>
</table>

Inject I.V. solutions in 3-4 minutes, within one hour following their preparation.

**Intermittent intravenous infusion**

Solutions should be prepared as described for intravenous injection and then added to an intravenous infusion solution in a mini-bag or in-line burette and administered over a period of 30-40 minutes. Alternatively, using a suitable reconstitution device, the appropriate volume of intravenous fluid may be transferred from the infusion bag into the vial and then drawn back into the bag after dissolution.

**Intramuscular injection**

<table>
<thead>
<tr>
<th>Vial strength</th>
<th>Recommended volume of Water for Injections BP to be added for dissolution</th>
<th>Final volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g</td>
<td>2 ml</td>
<td>2.7 ml</td>
</tr>
</tbody>
</table>

After addition of water to the vial, shake vigorously.
Inject I.M. solutions immediately after preparation.

The solutions should preferably be used as soon as possible after their preparation and, in any case, no later than the time indicated below if they are kept at a temperature not exceeding 25°C:

Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C for the following diluents:
- Physiological saline
- 10% Dextrose
- Sodium chloride compound (Ringer)
- Hartmann solution (sodium lactate + Ringer’s lactate)

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C for the following diluents:
- Water for injection
- 5% Dextrose
- Sodium lactate M/6
- Sorbitol
- Dextran

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

7  MARKETING AUTHORISATION HOLDER
   EUMEDICA SA
   Winston Churchill Avenue
   67 – 1180 Brussels
   Belgium

8  MARKETING AUTHORISATION NUMBER(S)
   21772/0001

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   22/11/2005
10 DATE OF REVISION OF THE TEXT

19/08/2011