Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Negaban 1 g powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Negaban 1 g
1 vial contains 1.11 g temocillin disodium, corresponding to 1 g temocillin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Negaban is indicated for the treatment of the following infections in adults and in children, where susceptible gram-negative bacilli are highly suspected or confirmed (see sections 4.2, 4.4 and 5.1):

- complicated urinary tract infections and acute pyelonephritis;
- lower respiratory tract infections (including hospital-acquired pneumonia);
- acute skin and soft tissue infections;
- bacteraemia that occurs in association with, or is suspected to be associated with, the licensed indications.

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

4.2 Posology and method of administration

The global information for both I.V. and I.M. routes is contained in this Summary of Product Characteristics. It is then needed to be cautious on the relevant information corresponding to the dose and the type of parenteral route.

Treatment should be started in a hospital setting.

Posology

The schedule regimen is determined according to the severity, the renal function of the patient and, in children the body weight.
After initiation of treatment, the treatment can be switched to oral treatment if clinically indicated at the discretion of the physician. Parenteral treatment should be followed by oral route as soon as possible.
Treatment of some infections may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.
Therapeutic guidelines should be adhered to.

Patients with normal renal function

Adults (including elderly)
Standard dose: 4 g per day to be divided into 2 administrations.
High dose notably in critically ill patients: 6 g per day to be divided into 3 administrations or as continuous infusion. A loading dose of 2 g should be administered before starting the continuous infusion (see Method of administration).

There are current uncertainties on the recommended posology.
Investigations are ongoing on the 6g/day in case of severe infections and/or involving multi-resistant strains (ESBL producing Enterobacteriaceae).

Paediatric population
25 to 50 mg per kg per day, to be divided into 2 administrations, with a maximum of 4 g/day. In case of severe infections, the highest dose is recommended (50 mg/kg per day).

There are current uncertainties on the recommended posology.
There are current uncertainties on the adequacy of the recommended lower posology of 25mg/kg/day in each indication. The appropriateness of this lower dose is currently under investigation as well as the need to exceed the 50 mg/kg/day in case of severe infections and/or involving multi-resistant strains (ESBL producing Enterobacteriaceae).

Population	Dosage per 24 hours		
	Standard dose	High dose *	
Adults	4 g in 2 administrations (2 g/12 h) (I.M., I.V. injections or infusion)	6 g in 3 administrations (2 g/8 h) (I.V. injections or infusion) or as continuous infusion (administer a loading dose of 2 g before starting the continuous infusion)	
	with possible complementary antibiotherapy		
Children			
	25 mg/kg/24 h in 2 administrations (I.M., I.V. injections or infusion)	50 mg/kg/24 h in 2 administrations (I.V. injections or infusion)	

** The high dose is mainly supported by PK/PD data with very limited clinical data. Further clinical data will be derived from ongoing investigations.*

Remark: Based on the available data, the use of the I.M. route should only be considered when the I.V. route is not feasible (the probability of PK/PD target achievement has not been assessed using this route of administration).

Patients with renal insufficiency

Posology must be reduced according to the severity of the renal insufficiency, established by values of creatinine clearance in accordance with the following diagram:

Creatinine clearance	Posology: Standard dose	
(mL/min)	Dosage per administration	Interval between administrations
more than 60	2 g	12 h
60 to 30	1 g	12 h
30 to 10	1 g	24 h

There are current uncertainties on the recommended posology in patients with renal insufficiency and appropriate adjustment to a higher dose in this population.

- *In case of intermittent high-flux haemodialysis*
In general, I.M. administration should be avoided, due to patient's heparinisation. It is recommended to inject Negaban by intravenous administration, using water for injection or physiological saline as solvent.
1 g (I.V. injection) per 24 h of inter-dialytic session, preferably at the end of haemodialysis (1 g q24 h, 2 g q48 h, 3 g q72 h).

- *In case of continuous peritoneal dialysis in ambulatory patient*
1 g NegabanI.M. every 24 h.

Patients with impaired liver function

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 or continuous intravenous infusion or intramuscular injection.

Intravenous solutions: Negaban may be administered by slow injection over 3 to 4 minutes, by intravenous infusion over a period of 30-40 minutes. Continuous intravenous infusion of temocillin 6 g daily might be considered in critically ill patients when therapeutic objectives are difficult to reach with intermittent administrations despite high dose level. A loading dose of 2 g should be administered before starting the continuous infusion. Continuous intravenous infusion of temocillin is mainly supported by PK/PD data with very limited clinical data.
Intramuscular injection: Negaban must be given intramuscularly after reconstitution. In case of pain at the site of I.M. injection, a solution of lidocaine may be used.

For instructions on reconstitution and/or dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to penicillins or to any other type of beta-lactam agent.

4.4 Special warnings and precautions for use

Consideration to the anti-microbiological activity of this antibiotic, to the prevalence of resistance to other antibacterial agents and to the therapeutic guidelines should be made before initiating a treatment with temocillin.

Hypersensitivity
Allergy to beta-lactams should be systematically researched in advance by a thorough anamnesis.
Careful enquiry should be made concerning hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (see sections 4.3 and 4.8).
Cross-allergy with cephalosporins is frequent (10 to 15 %).
Special caution is required in case of asthma or atopy history.

Serious and occasionally fatal anaphylactic reactions have been reported in patients receiving therapy with penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs during therapy with Negaban, the drug must be discontinued, and appropriate alternative therapy instituted.

Impaired renal function
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 case of renal insufficiency, dosages should be adapted to the extent of renal insufficiency, as recommended in section 4.2.

Clostridium difficile infection
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. Preparations which inhibit peristalsis are contra-indicated.

Follow-up
At the standard dosages, i.e., up to 4 g per day, the consequences on the blood platelets and kalaemia, and the occurrence of phlebitis and neurotoxic effects may be considered as very rare. However, should higher dosages be required, attention must be drawn to the possibility of such reactions.

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

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.

Resistance
As with any prolonged use of antibiotics, caution should be taken on any possible occurrence of super infections caused by non-sensitive species.

Sodium
Sodium content: 4.8 mEq. per g.

4.5 Interaction with other medicinal products and other forms of interaction

There is no antagonism with aminoglycosides, metronidazole, penicillins and cephalosporins.
Based on the general principle not to combine bactericidal and bacteriostatic antibiotics, it is recommended not to associate Negaban - as any other penicillin - with bacteriostatic anti-infectious medicines, due to possible antagonistic effect.

4.6 Fertility, pregnancy and lactation

Pregnancy
Data concerning the use of Negaban in pregnant women are insufficient to assess any possible harmfulness. Studies on animals have so far shown no evidence of harmfulness.
As a precautionary measure, it is preferable to avoid the use of Negaban during pregnancy.

Breastfeeding
Caution is also advised during breastfeeding. The possibility of hypersensitivity reactions should be considered in sensitive newborns.
Trace quantities of penicillins can be detected in the milk or lactating mothers.

Fertility
Studies on animals have not shown evidence of harmfulness.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Frequency not known (cannot be estimated from the available data)
Immune system disorders
Risk of allergic reactions, as with any beta-lactams:
- urticaria
- purpura
- fever
- eosinophilia
- maculo-papular rash
- sometimes Quincke's oedema
- much more rarely anaphylactic shock.

Some reactions such as fever, joint pain, myalgia sometimes appear more than 48 hours after the start of the treatment.
Please refer to section 4.4 for the treatment of anaphylactic shock.
In all cases, treatment must be discontinued, and a substitution treatment must be used.

Vascular disorders
As with some other injectable beta-lactams, although to a much lesser extent, after intravenous administration there is a risk of:
- phlebitis
- thrombophlebitis

Nervous system disorders
For patients suffering from renal insufficiency, neurological disorders with convulsions are sometimes reported after I.V. injection of high doses of penicillins.

General disorders and administration site abnormalities
Occasionally, intramuscular injection may be painful. In this case, it is recommended to use a 1% lidocaine solution as solvent.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via
HPRA Pharmacovigilance
Website: www.hpra.ie.

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: beta-lactam antibiotic, penicillins, ATC code: J01CA17

Mechanism of action
Negaban is a bactericide antibiotic, for parenteral use, belonging to the class of beta-lactams, acting by interference with the cell wall synthesis of micro-organisms.

The spectrum of Negaban covers most of aerobic Gram-negative micro-organisms, with the exception of *Pseudomonas aeruginosa* and *Acinetobacter*. It is not active against Gram-positives and anaerobic germs.

Negaban is not active against anaerobic flora and consequently provokes less disturbance of normal intestinal microbiota.

PK/PD relationship
Negaban has a bactericidal activity; minimal bactericidal concentrations are close to minimal inhibitory concentrations or are only two to four times higher.
Negaban shows a high stability towards chromosomal and plasmidic beta-lactamases; due to its rather long half-life (4.5 h), serum and tissue concentrations remain high enough to allow twice-daily posology.
Mean serum concentrations after administration of Negaban are given in section 5.2.

Mechanism of resistance
Thanks to the stability of Negaban towards almost all chromosomal and plasmidic beta-lactamases (including cephalosporinases), there is only a low incidence of resistant strains.

Strains of facultative Gram-negative germs resistant to 2nd and 3rd generation cephalosporins are often sensitive to Negaban because there is virtually no cross-resistance.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for temocillin and are listed here:
https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

National committees in France (Comité de l'Antibiogramme de la Société Française de Microbiologie CA-SFM) and Belgium (Société Belge d'Infectiologie et de Microbiologie Clinique/Belgische Vereniging voor Infectiologie en Klinische Microbiologie - Guide d'Infectiologie/Infectiologiegids SBIMC/BVIKM - IGGI) have established national criteria for susceptibility testing.
Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible organisms:
- *Escherichia coli*
- *Klebsiella pneumonia*
- *Citrobacter spp.*
- *Pasteurella multocida*
- *Proteus mirabilis*
- *Proteus spp (indole +)*
- *Providencia stuartii*
- *Legionella pneumophila*
- *Moraxella catarrhalis*

- *Salmonella Typhimurium*
- *Shigella sonnei*
- *Yersinia enterocolitica*
- *Brucella abortus*
- *Haemophilus influenzae*
- *Neisseria gonorrhoeae*
- *Neisseria meningitides*

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

Intrinsically resistant organisms:
- *Pseudomonas aeruginosa*
- *Acinetobacter spp.*
- Anaerobics
- Gram-positives

5.2 Pharmacokinetic properties

Resorption
Negaban ensures high and sustained serum concentrations of temocillin:

Administration	Mean serum concentrations (mg/L)	Mean serum concentrations (mg/L)	Mean serum concentrations (mg/L)	Percentage collected in urine within 24 hours
	Serum peak	after 6 h	after 12 h	
Injection I.M. 1 g	70 after 2 h	40	18	78%
Injection I.V. 1 g	172	25	12	72%
Injection I.V. 2 g	269	47	16	79%

Distribution
The binding rate to serum proteins depends on the plasma concentration of temocillin. At 16 mg/L it is approximately 85%. Sustained concentrations of temocillin are obtained in prostatic tissue, interstitial liquid, lymphatic liquid and lung. After administration of Negaban, the following mean concentrations were observed:

Peripheral lymph	1 g I.V.	after 1 hour : 14.3 mg/L after 2 hours : 30.6 mg/L
Prostate	2 g I.V.	after 2 hours : 37.9 µg/g
Interstitial liquid (derived from cantharidine-induced skin blisters)	1 g I.V.	after 1 hour : 37.1 mg/L after 3 hours : 44.3 mg/L
Lung	2 g I.V.	after 30 min : 45 mg/kg

Only very small amounts of temocillin pass in the cephalo-rachidian liquid, except in case of meningitis.

Elimination
Half-life is very long in comparison to other pencillins:
- I.V. injection: 4.5 hours
- I.M. injection: 5.4 hours

Temocillin metabolisation may be considered as not significant. Temocillin is eliminated mainly by tubular excretion. About 80% of the administered dose is eliminated unchanged in 24 hours by the kidneys.
After I.M. injection of 1 g temocillin, urinary concentrations over 1,300 mg/L are observed in subjects with normal renal function.

Renal impairment
Excretion may be delayed in case of renal insufficiency. In a study performed in patients with end-stage renal disease, the elimination half-life (median, 24-26h) was prolonged. 48% to 59% of the residual concentration was removed by intermittent haemodialysis.

5.3 Preclinical safety data

The non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, mutagenic toxicity and toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Negaban may not be dissolved in solutions of sodium bicarbonate, proteins or proteins hydrolysates and lipids, or in blood or plasma.

Should Negaban be simultaneously administered with an aminoglycoside, both antibiotics may not be mixed in the syringe or in the recipient containing the infusion solution because there is a risk of loss of activity.

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

6.3 Shelf life

Unopened vials: 3 years

Reconstituted and diluted solutions: refer to details on appropriate solvents and administration times to section 6.6.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C for all the solvents recommended for intravenous infusion.

From a microbiological point of view, the product should be used immediately.

6.4 Special precautions for storage

Unopened vials: Store and transport refrigerated (2°C-8°C).

Reconstituted and diluted solutions: Do not refrigerate. See further under sections 6.3 and 6.6.

6.5 Nature and contents of container

Negaban 1 g: box containing 1 vial.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused solution.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Preparation of solution and administration of Negaban

Standard aseptic techniques should be used for solution preparation and administration.

The solutions should be visually inspected prior to use. Only clear solutions practically free from particles should be used.

The product should always be used immediately after reconstitution and dilution.

Dose	**Suitable solvents**	**Preparation of solution and administration**

Intramuscular injection		
1 g	Water for injection Physiological saline 0.5 or 1% lidocaine solution. Lidocaine solution should not be administered intravenously.	To prepare the 1 g dose, introduce a syringe needle through the vial closure and inject 3 mL of solvent in 1 vial of Negaban 1 g. Withdraw the needle and shake the vial to obtain a clear solution. Administer immediately after preparation.
Intravenous injection		
1 g or 2 g	Water for injection Physiological saline	To prepare a 1 g dose, introduce a syringe needle through the vial closure and inject 10 mL of solvent in 1 vial of Negaban 1 g. To prepare a 2 g dose, introduce a syringe needle through the vial closure and inject 20 mL of solvent in 1 vial of Negaban 2 g. Withdraw the needle and shake the vial to obtain a clear solution. Administer in 3 to 4 minutes.
Intermittent intravenous infusion		
1 g or 2 g	Water for injection Physiological saline (0.9% sodium chloride) Dextrose 5% Sodium chloride compound (Ringer's solution) Hartmann (Sodium lactate compound – Ringer's lactate solution)	To prepare the 1 g dose, introduce a syringe needle through the vial closure and inject 10 mL of solvent in 1 vial of Negaban 1 g. To prepare the 2 g dose, introduce a syringe needle through the vial closure and inject 20 mL of solvent in 1 vial of Negaban 2 g. Withdraw the needle and shake the vial to obtain a clear solution. Dilute into a 50-, 100- or 150-mL solution for infusion. Administer in 30 to 40 minutes.
Continuous infusion		
6 g	Water for injection Physiological saline (0.9% sodium chloride) Dextrose 5% Sodium chloride compound (Ringer's solution) Hartmann (Sodium lactate compound –	Negaban 1 g: introduce a syringe needle through the vial closure and inject 5 mL of solvent in each of 6 vials. Negaban 2 g: introduce a syringe needle through the vial closure and inject 10 mL of solvent in each of 3 vials. Withdraw the needle and shake the vial to obtain a clear solution. Using a syringe of 50 mL, collect all solutions from the vials and bring the volume to 48 mL with the same solvent. Administer the solution over 24 h (2 mL/h). Note: A loading dose of 2 g temocillin is required before starting the continuous infusion.

	Ringer's lactate solution)	

7 MARKETING AUTHORISATION HOLDER

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