SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oxacillin AVMC 1000 mg powder for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial with powder for solution for injection/infusion contains oxacillin 1000 mg (as oxacillin sodium monohydrate).
Each vial contains approximately 64 mg (2.8 mmol) sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion
White or almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oxacillin AVMC is indicated for adults and children for the treatment of staphylococcal infections with strains susceptible to oxacillin (see also section 5.1):
- Endocarditis;
- Meningitis;
- Pneumonia;
- Bone and joint infections;
- Osteomyelitis;
- Bacteraemia associated with or suspected to be associated with the above infections
- Staphylococcal and/or streptococcal skin infections with strains susceptible to oxacillin;
- Prophylaxis of postoperative infections (including neurosurgery procedures, plastic surgery etc).

Treatment guidelines in force on the appropriate use of antibiotics should be considered.

4.2 Posology and method of administration

Posology
Several dosage schemes exist, depending on the target group (e.g., adults, elder, children, neonates), the type of infection (e.g., endocarditis, meningitis, pneumonia, skin soft tissue infections etc.), the recommended dosage is the following:

Adults
Bacterial Infection

Mild-to-moderate infections:	250 to 500 mg IV or IM every 4 to 6 hours
Severe infections:	1 g IV or IM every 4 to 6 hours

Endocarditis
Native valve infective endocarditis: 2 g IV every 4 hours or 3 g IV every 6 hours. Prosthetic valve endocarditis: 2 g IV every 4 hours. Total dose: 12 g/day
Duration of Therapy: For complicated right-sided native valve endocarditis and for left-sided native valve endocarditis: 6 weeks. For uncomplicated right-sided native valve endocarditis: 2 weeks. For prosthetic valve endocarditis: At least 6 weeks.

Joint Infections
1.5 to 2 g IV every 4-6 hours

Meningitis
1.5 to 2 g IV every 4 hours
Osteomyelitis
1.5 to 2 g IV every 4-6 h. Duration of therapy: 6 weeks

Skin or Soft Tissue Infection
Incisional surgical site infections: 2 g IV every 6 h.
Skin and soft tissue infection, necrotizing infections: 1 to 2 g IV every 4 h

Paediatric population
Premature and neonates: 12,5 mg/kg IV or IM every 8-12 hours
Infants and children weighing <40 kg:
Mild to moderate infections: 12.5 mg/kg IV or IM every 6 h
Severe infections: 25 mg/kg IV or IM in every 4-6 h
Children weighing at least 40 kg:
Mild to moderate infections: 250 to 500 mg IV or IM every 4-6 h.
Severe infections: 1 g IV or IM every 4-6 h.

Endocarditis
1 year or older: 50 mg/kg IV every 4 to 6 hours. Maximum dose: 12 g/day. Duration of therapy: At least 4 to 6 weeks

Meningitis
Neonates 0 to 7 days: 25 mg/kg IV every 8 to 12 hours.
Neonates 8 to 28 days: 50 mg/kg IV every 6 to 8 hours.
Infants and children: 50 mg/kg IV every 6 hours. Maximum dose: 12 g/day

Pneumonia
Infants and children older than 3 months: 50 mg/kg IV or IM every 6 to 8 hours. Maximum dose: 12 g/day

Skin or Soft tissue infection
1 month or older:
Necrotising infections: 50 mg/kg IV every 6 hours.
Skin and soft tissue infection: 25 – 37.5 mg/kg IV every 6 hours

Staphylococcal Infections

Age group	**Weight**	**Dosage**
Neonates <1 week of age	<1.2 kg	25 mg/kg every 12 hours
	1.2 to 2 kg	25-50 mg/kg every 12 hours
	> 2 kg	25-50 mg/kg every 8 hours

Neonates 1-4 weeks of age	<1.2 kg	25 mg/kg every 12 hours
	1.2 to 2 kg	25-50 mg/kg every 8 hours
	> 2 kg	25-50 mg/kg every 6 hours

Elderly
With IV administration, particularly in elderly patients, care should be taken because of the possibility of thrombophlebitis.

Renal impairment
In patients with severe renal impairment (CL_{Cr} < 10 mL/min) dose adjustment is required. The creatinine clearance should be considered, and monitoring of drug levels is highly recommended (see section 4.4).

Treatment should continue for at least 48 hours after resolution of signs and symptoms of infection.

Method of administration:
Oxacillin is administered by intramuscular (IM) deep injection, IV injection and, eventually, intravenous (IV) infusion after reconstitution with a compatible solvent. For the preparation of the injectable solutions see section 6.6.

IV infusion:
The concentration of antibiotic should be between 0.5 and 2 mg / ml. The drug concentration, infusion rate and volume should be adjusted so that the total dose of oxacillin is administered before the drug loses its stability in solution for use.

IV injection
Solution should be used immediately after preparation, injecting it slowly IV in 10 minutes to reduce risk of thrombophlebitis and other adverse local reactions associated with IV administration (particularly in geriatric patients). Administer slowly and take care to avoid extravasation.

IM injection should be administered deep in the muscle.

4.3 Contraindications

Hypersensitivity to oxacillin, other penicillins or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Risk of hypersensitivity reactions:
Immediate hypersensitivity reactions (anaphylaxis) to penicillins or cephalosporins may be serious and sometimes potentially lethal. Severe anaphylactic reactions require immediate intervention including administration of epinephrine, fluids and steroids, oxygen, airway management, or intubation.

Before initiation of the treatment a careful anamnesis is necessary in order to highlight the history of hypersensitivity to cephalosporins, penicillins, other beta-lactam antibiotics or other allergens. It should be considered the risk the occurrence of cross-hypersensitivity reactions with other beta-lactams. The occurrence of any allergic reactions requires discontinuation of therapy

Hyperbilirubinemia:

Oxacillin displaces bilirubin from the albumin-binding site. Therefore, caution is advised in case of the treatment with oxacillin in neonates with hyperbilirubinemia. Oxacillin should not be administered in neonates (especially premature infants) at risk of bilirubin encephalopathy.

Severe renal impairment:
In patients with severe renal impairment (creatinine clearance < 10 mL/min), the dose of oxacillin should be adjusted according to creatinine clearance (see section 4.2).

Clostridioides difficile-associated disease
Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with oxacillin (including several weeks after treatment), may be symptomatic of Clostridioides difficile-associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis (see section 4.8). It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with oxacillin. If CDAD is suspected or confirmed, ongoing treatment with antibacterial agents, including oxacillin should be stopped immediately and appropriate treatment initiated without delay. Anti-peristaltic medicinal products are contraindicated in this clinical situation. Furthermore, appropriate infection control measures should be undertaken to reduce the risk of transmission.

Pediatric population
In neonates, the renal elimination mechanisms are not fully developed, thus, penicillinase-resistant penicillins (especially methicillin) may not be completely eliminated, which may result in abnormally high blood levels. Therefore, frequent monitoring of blood antibiotic levels and dose adjustment are recommended when administering oxacillin to neonates. All neonates treated with penicillin should be closely monitored for adverse signs and/or laboratory or clinical signs of toxicity.

Other precautions:
Similar to other antibiotics, prolonged administration of oxacillin may lead to the selection of some resistant bacterial strains.
In case of long-term treatment, periodic monitoring of blood counts blood urea nitrogen and creatinine determinations is recommended. Dosage alterations should be considered if these values become elevated.
When glucosuria is tested by non-enzymatic methods, oxacillin may cause false-positive results (see section 4.5).
Oxacillin should not be mixed in the same syringe, infusion bottle or infusion bag with other medicines (see section. 6.2).

Patients on a low sodium diet:
This medicinal product contains 64 mg sodium per vial, equivalent to 3.2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Administration of antibiotics in combination with vaccines with attenuated germs may decrease the efficacy of vaccines.

Administration of oxacillin in combination with methotrexate determines the increase of haematologic toxic effects of methotrexate and inhibits the renal tubular secretion.

Certain medicines may decrease the effectiveness of oxacillin: cholestyramine, other antibiotics (e.g. erythromycin, tetracycline, doxycycline).

In patients receiving antibiotics, especially penicillinase-resistant penicillins, cases of increase of the activity of oral anticoagulants have been reported. Infectious and inflammatory context, age and general condition of the patient are risk factors.

There are relations of antagonism between oxacillin and rifampicin.

Probenecid and mezlocillin inhibit the renal excretion of oxacillin.

Oxacillin may cause intensification of the undesirable effects of allopurinol, causing transient cutaneous eruptions.

When glucosuria is tested by non-enzymatic methods, oxacillin may cause false-positive results (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Although preclinical studies did not show teratogenic or foetotoxic effects, oxacillin should be administered with caution in pregnant women. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on fetus.
There are, however, no adequate or well-controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Breastfeeding
Limited information indicates that oxacillin produces low levels in milk that are not expected to cause adverse effects in breastfed infants. Occasionally disruption of the infant's gastrointestinal flora, resulting in diarrhoea or thrush have been reported with penicillins. Oxacillin is acceptable in nursing mothers.

Fertility
Animal reproduction studies have revealed no evidence of impaired fertility. Clinicians must take into account that treatment with antibiotics may adversely affect the fertility potential of men. It is possible that some classes of antibiotic agents, such as the penicillins, may have minimal effects on male fertility and maintain the clinical efficacy for patients requiring long-term antibiotic suppressive therapy.

4.7 Effects on ability to drive and use machines

Oxacillin AVMC has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Within each frequency group, the undesirable effects are presented in decreasing order of frequency: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10000), or frequency not known.

Blood and lymphatic system disorders:
Not known: anaemia, thrombocytopenia, leukopenia, which are reversible with discontinuation of treatment.

Immune system disorders:
Very rare: anaphylactic shock
Not known: fever, rash, eosinophilia, Quincke oedema.

Nervous system disorders:
Not known: The administration of high-dose of beta-lactams, particularly in patients with renal insufficiency, can cause encephalopathy (disorders of consciousness, abnormal movements, and convulsions).

Gastrointestinal disorders:
Very rare: pseudomembranous colitis.
Not known: nausea, vomiting, diarrhoea.

Hepatobiliary disorders:
Rare: increased serum values of transaminases and exceptionally hepatitis with jaundice may occur.

Renal and urinary disorders:
Not known: immunoallergic acute interstitial nephropathy.

General disorders and administration site conditions
Not known: fatigability.

Infections and infestations
Not known: fungal superinfection (vaginal candidiasis).

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 the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms of overdose include muscle spasms, convulsions, pain and loss of sensitivity in the fingers, bleeding, confusion, coma, agitation. Toxic phenomena are favoured by renal impairment. Treatment is symptomatic and supportive. Oxacillin cannot be removed to a significant degree by hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: beta-lactam antibacterials, penicillins, beta-lactamase resistant penicillins, ATC code: J01CF04.

Mechanism of action

Oxacillin is semi-synthetic penicillin belonging to the group of isoxazolyl penicillins. Like all penicillins oxacillin inhibits the biosynthesis of the bacterial cell wall. Oxacillin binds to penicillin-binding proteins in the bacterial cell wall, thereby blocking the synthesis of peptidoglycan, a critical component of the bacterial cell wall.
Penicillins belonging to the group of isoxazolyl groupare effective in infections caused by most of staphylococci, which is why they are also called antistaphylococcal penicillins.

Due to the bulky chain present in the molecule, oxacillin is resistant to the hydrolytic action of penicillinase, the beta-lactamase secreted by staphylococci resistant to penicillin G (the stereochemical protection prevents the enzyme to reach the beta-lactam nucleus and to break it).

PK PD relationship
Beta-lactam antibiotics, thus also oxacillin, display 'time-dependent' activity, which is optimal when the duration of time (*T*) that the free drug concentration remains above the minimum inhibitory concentration (MIC) during a dosing interval ($fT_{>MIC}$) is at least 40-70%. However, further data suggested that patients may benefit from higher, and longer (e.g. 100% $fT_{>MIC}$), beta-lactam exposures than those described in early preclinical infection models.

Mechanism of resistance
Microorganisms that elaborate penicillinases tent to be resistant to very high levels of antibiotic. The production of penicillinase by staphylococci is controlled by an extrachromosomal piece of deoxyribonucleic acid (DNA) which is passed "horizontally" through the colony.
Resistance can occur by multiple mechanisms, including modification of the target (mutation or expression of alternative penicillin binding proteins), reduction in cell permeability through downregulation of porins required for beta-lactam entry, overexpression of efflux systems and production of modifying or degradative enzymes. In the case of beta-lactams, enzyme-mediated resistance arises from the activity of beta-lactamases, enzymes produced by both Gram-positive and Gram-negative bacteria that hydrolyse the β-lactam amide.

Antimicrobial activity
The antibacterial spectrum of oxacillin is similar to that of penicillin G, but the susceptibility of germs is lower; minimum inhibitory concentration MIC for penicillinase-negative staphylococci and streptococci (except pneumococci) are higher. Enterococcus and Gram-negative germs are less susceptible.

5.2 Pharmacokinetic properties

Absorption
After 30 minutes from the IM administration of a dose of 250 mg oxacillin the plasma concentration is of about 5.3 μg/mL. After the IV administration of the same dose, the plasma concentration after 5 minutes is the maximum.
After 30 minutes from IM administration of a dose of 500 mg oxacillin the plasma concentration is of about 11 μg/mL. After the IV administration of the same dose, the plasma concentration after 5 minutes is 43 μg/mL. After 6 hours, the antibiotic is no longer detectable in the blood.

Distribution
After IM/IV administration of a dose of 1000 mg oxacillin peak plasma concentrations are approximately 15 μg/mL, 2 times higher than after oral administration are reached.
Oxacillin binds to plasma proteins in an extent of approximately 90 %.
Oxacillin diffuses in all tissues of the body, especially in the amniotic fluid and in the fetal blood.

Biotransformation
Oxacillin is partially metabolised in the liver.

Elimination
Oxacillin and it's metabolites is excreted by renal excretion by approximately 50% of the administered dose (tubular secretion and glomerular filtration) and also in the bile (in a negligible extent). Elimination half-life is about 0,4-0,7 h., more prolonged in neonates and in patients with renal impairment.
Purging is done by metabolism (45 % of dose) and by renal excretion (46%).

5.3 Preclinical safety data

Animal studies have shown no teratogenic or fetotoxic effects.

Environmental risk assessment studies have shown that oxacillin may pose a risk for the aquatic environment (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous disodium phosphate.

6.2 Incompatibilities

Oxacillin is incompatible with aminoglycosides and tetracyclines. As a general rule, it is not recommended to mix oxacillin with other drugs in the same syringe, infusion bottle or infusion bag.

6.3 Shelf life

3 years

After reconstitution:
Intravenous injection (100 mg/ml)
Oxacillin powder for solution for injection/infusion (1g/vial) is reconstituted with 10 ml of water for injection or 10 ml of 0.9% sodium chloride solution to the concentration 100 mg/ml.

Intramuscular injection (167 mg/ml)
Oxacillin powder for solution for injection/infusion (1g/vial) is reconstituted with 5.7 ml of water for injection or 5.7 ml of 0.9% sodium chloride solution to the concentration 167 mg/ml.

After reconstitution and dilution:
Intravenous infusion (0.5 mg/ml or 2.0 mg/ml)
Oxacillin powder for solution for injection/infusion (1g/vial) is reconstituted with water for injection or/Isotonic sodium chloride solution and diluted with different solvents and at different final concentrations (0.5 and 2.0 mg/ml).

Chemical and physical in-use stability (as reconstituted for injection or reconstituted and diluted for infusion as described above) has been demonstrated for 8 hours at 2 – 8 °C.

From microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior use are the responsibility of the user.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Box with 1, 10, 25 or 50 clear glass vial(s), type III, containing powder corresponding to Oxacillin 1000 mg, closed with grey chlorobutyl rubber stopper and sealed with aluminium flip-off cap.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For intramuscular (IM) administration
For the preparation of injectable solution administered intramuscularly add into the vial 5.7 mL of water for injections or 0.9% sodium chloride solution. Shake the vial until a clear solution without any yellowish coloration is obtained. It is administered by deep IM.

For intravenous (IV) administration
the preparation of injectable solution administered intravenous add into the vial 10 mL of water for injections or 0.9% sodium chloride solution. Shake the vial until a clear solution without any yellowish coloration is obtained.
The solution should be administered by slowly IV injection in 10 minutes to reduce risk of thrombophlebitis and other adverse local reactions associated with IV administration (particularly in geriatric patients). Administer slowly and take care to avoid extravasation.

I.V. infusion:
The infusion solution is prepared in the same manner as for the intravenous administration and it is diluted in various infusion solutions.
Before dilution with the infusion solution, the powder is reconstituted according to the instructions given for I.V. submission. The concentration of antibiotic should be between 0.5 and 2 mg / ml.

The reconstituted solution is further diluted with one of the following solutions for infusion:
- isotonic sodium chloride solution
- 5% glucose solution in water for injections
- 5% glucose solution in isotonic sodium chloride solution
- 10% solution of D-fructose in water for injections
- 10% solution of D-fructose in isotonic sodium chloride solution
- Ringer's solution for infusion with lactate
- solution for injection of potassium chloride and sodium chloride with lactate
- 10% solution of invert sugar in water for injections
- 10% solution of invert sugar in isotonic sodium chloride solution
- 10% solution of invert sugar + 0.3% of potassium chloride in water for injections

Only these solutions should be used for I.V. infusion of Oxacillin AVMC 1 g.

The reconstituted solution should be inspected visually for particulate matter and discolouration prior to administration. The solution should only be used if it is clear and free from particles.

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<To be completed nationally>

8. MARKETING AUTHORISATION NUMBER(S)

<To be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<To be completed nationally>

10. DATE OF REVISION OF THE TEXT

<To be completed nationally>