SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Cloxacillin 0.5g powder for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains cloxacillin sodium equivalent to 0.5 g cloxacillin.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion

White crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cloxacillin is indicated for the treatment of infections due to penicillinase producing staphylococci: Skin and soft tissue infections, endocarditis, abscesses, osteomyelitis and sepsis.

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

4.2 Posology and method of administration

Adults:

Intramuscular*:* 0.5 - 1 g 4 times/24 hours. The solution should be administered as deep intramuscular injection. Intramuscular injection is not recommended for severe infections.

Intravenous injection:

1-2 g 3-4 times/24 hours. The solution should be given steadily, at least 3-4 minutes per g, if possible in a large vein.

Intravenous intermittent infusion (short time infusion): 2 g 4 (-6) times/24 hours. The solution should be given steadily as an infusion over 20(-30) minutes.. Continuous intravenenous infusion: The usual dose is 6 g/24 hours. In serious infections, such a dose can be increased to 12 g/24 hours.

Children:

Intramuscular: 50 mg/kg/24 hours divided into 4 doses. Intravenous: 100 mg/kg/24 hours (or more) divided over 4-6 doses.

Endocarditis:

1 g 6 times daily or 2 g 4 times daily. Cloxacillin should be given in combination with an aminoglycoside during the first week of treatment. In serious cases the dose can be increased to 12 g/24 hours, given as 2 g 6 times daily alternatively 12 g/24 hours as

continuous infusion.

Severe kidney insufficiency:

Elimination of cloxacillin is reduced in severe renal insufficiency. Due to low toxicity dosage adjustment is usually not necessary. Nevertheless, very high doses should be avoided unless clinically necessary and symptoms of toxicity should be monitored (see section 4.9).

Parenteral therapy is indicated in cases where the patients are unable to take an isoxazolylpenicillin orally, as well as in advanced cases where there is a need to obtain high serum concentrations rapidly. Due to low toxicity very high doses can be given, if required, without increased risk for adverse drug reactions. For osteomyelitis and other conditions where there are difficult to reach sufficient antibiotic concentrations in the infected area, the treatment should, according to the need, last for months or years. This implies that initial intravenous therapy should be replaced with a peroral isoxazolylpenicillin.

4.3 Contraindications

Penicillin allergy and type 1 reaction to cephalosporines.

4.4 Special warnings and special precautions for use

In cases of severe reduced kidney function the dosage should be adjusted (see section 4.2).

Before initiating therapy with cloxacillin, careful enquiry should be made concerning previous hypersensitivity reactions to penicillin's and cephalosporins.

Neurological reactions, such as seizures, may occur when high doses are given to patients with severe kidney insufficiency or a defect blood-brain barrier. In such cases, the dosages should be reduced.

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all antibacterial agents, including cloxacillin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents. Discontinuation of therapy with cloxacillin and the administration of specific treatment for clostridium difficile should be considered. Medicinal products that inhibit peristalsis should not be given.

4.5 Interaction with other FPPs and other forms of interaction

Probenecid:

Concomitant administration of probenecid inhibits the tubular secretion of penicillin.

Oral contraceptives (The"Pill"):

Penicillines may very rarely reduce the absorption and hence the effect of oral contraceptives.

Methotrexate:

Concomitant use of methotrexate may give increased efficacy/toxicity of methotrexate due to reduced elimination.

Dicumarol medicinal products:

The efficacy of warfarin/dicumarol may be reduced with concomitant treatment with cloxacillin. The combination may require dose adjustment.

4.6 Pregnancy and lactation

Pregnancy

Long time clinical experience indicates little risk of adverse effects on pregnancy, or on the health of the foetus/new-born child.

Lactation

The product is to a low extent excreted in breast milk. Effects on suckling children are not likely, although the risk of influence on the childs intestine- and mouth flora cannot be excluded. Small amounts of the active substance in breast milk may increase the risk of sensibilization.

Fertility

No data are available.

4.7 Effects on ability to drive and use machines

It is unlikely that Cloxacillin can affect the ability to drive a car or to use machines.

4.8 Undesirable effects

Common (>1/100, <1/10)	*Gastrointestinal disorders:* Malaise, soft stool *Skin and subcutaneous tissue disorders:* Exanthema *General disorders and administration site conditions*:Thrombophlebitis (after intravenous injection)
Uncommon (>1/1,000, <1/100)	Blood and lymphatic system disorders: Eosinophilia Skin and subcutaneous tissue disorders: Urticaria
Rare (>1/10,000, <1/1,000)	*Blood and lymphatic system disorders*: Agranulocytosis, leucopeni *Gastrointestinal disorders*: Pseudomembraneous colitis *Hepatobiliary disorder:* Cholestatic liver damage. Renal and urinary damage: Kidney damage increased serum creatinine. General disorders and administration site conditions: Anaphylactic reactions.

Local pain can occur after intramuscular injection.

Overgrowth of yeast in the oral cavity and female genital tract may occur.

4.9 Overdose

Large doses are generally well tolerated. However, in cases of impaired renal function and defect blood/cerebrospinal fluid barrier, toxic symptoms due to parenteral administration have been reported. Acute reactions are primary due to hypersensibilisation.

Symptoms: Toxic reaction; malaise, vomiting, diarrhoea, change in electrolyte concentration, coma, muscle fasciculation's, myoclonia, cramps, coma, haemolytic reaction, kidney insufficiency, acidosis.

In rare cases anaphylactic reaction may occur within 20-40 minutes.

Treatment: Symptomatic treatment. In severe cases haemoperfusion or haemodialysis.

At anaphylactic reaction: Adrenalin (epinephrin) 0.3-0.5 mg intramuscular or 0.1-0.5 mg slowy intravenous. Sufficient intravenous fluid therapy. Intravenous corticosteroids (e.g. hydrocortison 200-1000 mg i.v.). If necessary, antihistamines (e.g. prometazin 25 mg intramuscuar or intravenous).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-lactamase resistant penicillin's.
ATC code: J01CF02

Mode of action
Cloxacillin Stragen belongs to the group isoxazolyl penicillin's, which is active against betalactamase- producing staphylococci with acid stability. Cloxacillin inhibits the synthesis of the bacterial cell wall. The effect is bactericidal.

Antibacterial spectrum

Commonly susceptible species

Staphyloccoccus aureus inclusive beta-lactamase-producing species.

Streptococci

Pneumococci.

<u>Species for which acquired resistance may be a problem</u>

Coagulats-negative stahpylococci

Inherently resistant species

Meticillin-resistant staphylococci

Enterococci

Gram-negative bacteria

Clostridium difficile

Resistance is common (approx 40%) in coagulase-negative staphylococci because of meticillin resistance.

Streptococci and pneumococci are more susceptible for benzyl-penicillin and penicillin V than for cloxacillin.

Mechanisms of resistance

Resistance against isoxazolyl penicillin's (so-called meticillin resistance) is caused by the bacteria producing a changed penicillin-binding protein. Cross resistance occurs in the beta-lactam group (penicillin's and cefalosporins). Meticillin-resistant staphylococci generally have low susceptibility for all beta-lactam antibiotics.

Development of resistance

In Scandinavia the level of methicillin resistance in Staphylococcus aureus is rather low, but more common in major parts of Europe. 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 east some types of infections is questionable.

5.2 Pharmacokinetic properties

Absorption

Following oral dose of 500 mg, a maximum plasma concentration of about 10 μg/ml (21 μmol/l) in fasting individuals is attained within 1 – 2 hours. Absorption is more complete when intramuscular injection is administered and maximum plasma concentration of about 15 μg/ml is administered 30 minutes after a dose of 500 mg.

Protein binding: 92%

Distribution

Provides good concentration in synovial fluid, urine and gall bladder.

Therapeutic serum concentration: Therapeutic level of about 1 μg/ml (2.1 μmol/l) is maintained for about. 4 hours.

Elimination

Half life in serum is about 30 minutes.

Excretion

Within 6 hours 30 – 50% of the oral dose is excreted in the urine. 10% is secreted as active metabolites in the urine.

5.3 Preclinical safety data

Preclinical data indicate no special risk for humans based on conventional studies of

safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential or toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Non known.

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

6.3 Shelf life

- Shelf-life of the product as packaged for sale: 3 years

- Shelf-life after dilution or reconstitution according to directions: After reconstitution, Cloxacillin sodium for Injection should be used immediately. Any unused portion must be discarded.

- Shelf-life after first opening of container: Not applicable

6.4 Special precautions for storage

Store below 30°C away from light and humidity. Keep out of reach of children.

For storage conditions after reconstitution/dilution see section 6.3.

6.5 Nature and contents of container

Cloxacillin sodium for injection 0.5g is contained in clear molded glass vials, capacity 7 ml, stoppered with butyl rubber stoppers and capped with aluminium caps.

Each pack contains 50 vials.

6.6 Instructions for use and handling

Intramuscular injection: Dilute 500 mg in 2 ml water for injection and 2 g in 4 ml water for injection.

Intravenous injection: Dilute 500 mg in 10 ml water for injection, 1 g in 20 ml water for injection and 2 g in 40 ml water for injection.

Intermittent infusions: Dilute 2 g in a 100 ml sodium chloride solution 9 mg/ml, or 100 ml water for injection.

Reconstitution of the powder or preparation of solution for infusion must be performed under aseptic conditions.

7. MARKETING AUTHORISATION HOLDER

Name: North China Pharmaceutical Co., Ltd.

Address: No.388 Heping East Road, Shijiazhuang, Hebei Province, China

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

N085/11

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/05/2019

10. DATE OF REVISION OF THE TEXT

10/07/2023