



Public Assessment Report

from the Norwegian Medicines Agency

Cloxacillin Stragen 1 g powder and solvent
for solution for injection / infusion

Cloxacillin Stragen 2 g powder and solvent
for solution for injection / infusion

Stragen Nordic AS, Denmark
cloxacillin sodium

MA-number in Norway: 04-2426 (1 g), 04-2426 (2 g)

Date: 2007-03-02

This assessment report is published by the Norwegian Medicines Agency (NoMA) following Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier which was submitted to the NoMA and its fellow organisations in all concerned EEA member states. It reflects the scientific discussion between the NoMA and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval and issue of a marketing authorisation.

This assessment report will be updated by an addendum whenever new important information becomes available.

Module 1: Information about the initial procedure

Module 2: Summary of product Characteristics (SPC)

Module 3: Package Leaflet

Module 4: Scientific discussion

Module 5: Update

Module 1: Information about the initial procedure:

1. Type of application: Abridged application according to Directive 2001/83/EC as amended, Article 10(1) generic application, claiming essential similarity.
2. Active substance: Cloxacillin sodium
3. Pharmaceutical form: Powder and solvent for solution for injection / infusion
4. Strength: 1 g and 2 g
5. MA holder: Stragen Nordic A/S, Møllehaven 8, DK-4040 Jylling, Denmark
6. Reference Member State: Norway
7. Concerned Member States: Sweden, Finland
8. Procedure-number: : NO/H/118/001-002/MR
9. Timetable:
Start (Day 0): 30.03.06
End (Day 90): 28.06.06

Module 2: Summary of product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Cloxacillin Stragen, 1 g & 2 g powder for solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cloxacillin sodium corresponding to 1 g or 2 g cloxacillin.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection / infusion

The product is a white or almost white crystalline powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cloxacillin Stragen is indicated for the treatment of infections due to penicillinase producing staphylococci: Skin and soft tissue infections, endocarditis, 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 intravenous 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 isoxazolympenicillin 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 isoxazolympenicillin.

4.3 Contraindications

Penicillin allergy and type 1 reaction to cephalosporines.

4.4 Special warnings and 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 medicinal products 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 child's intestine- and mouth flora cannot be excluded. Small amounts of the active substance in breast milk may increase the risk of sensibilization.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Common (>1/100, <1/10)	<i>Gastrointestinal disorders:</i> Malaise, soft stool <i>Skin and subcutaneous tissue disorders:</i> Exanthema <i>General disorders and administration site conditions:</i> Thrombophlebitis (after intravenous injection)
Uncommon (>1/1,000, <1/100)	<i>Blood and lymphatic system disorders:</i> Eosinophilia <i>Skin and subcutaneous tissue disorders:</i> Urticaria
Rare (>1/10,000, <1/1,000)	<i>Blood and lymphatic system disorders:</i> Agranulocytosis, leucopeni <i>Gastrointestinal disorders:</i> Pseudomembraneous colitis <i>Hepatobiliary disorder:</i> Cholestatic liver damage. <i>Renal and urinary damage:</i> Kidney damage increased serum creatinine. <i>General disorders and administration site conditions:</i> 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 slow intravenous. Sufficient intravenous fluid therapy. Intravenous corticosteroids (e.g. hydrocortison 200-1000 mg i.v.). If necessary, antihistamines (e.g. prometazin 25 mg intramuscular 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 beta-lactamase-producing staphylococci with acid stability. Cloxacillin inhibits the synthesis of the bacterial cell wall. The effect is bactericidal.

Antibacterial spectrum

Commonly susceptible species
Staphylococcus aureus inclusive beta-lactamase-producing species.
Streptococci
Pneumococci.

Species for which acquired resistance may be a problem

Coagulase-negative staphylococci

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 cephalosporins). 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 least some types of infections is questionable.

5.2 Pharmacokinetic properties

Distribution: Proteinbinding: 92%. Provide good concentrations in synovial fluid, urine and bile.
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 about 30 minutes. Excretion: In 6 hours is 30-50% the oral dose is excreted in urine. 10% is excreted as active metabolite 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

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

6.6.

6.3 Shelf life

3 years.

Reconstituted solution: The products should be used immediately.

6.4 Special precautions for storage

This drug requires no specific storage conditions.

The chemical and physical in-use stability has been demonstrated for 6 hours at room temperature (25 °C) at room light and 24 hours at 2 °C to 8 °C protected from light. .

From a microbiological point of view, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

1 g powder for solution for injection / infusion:

20 ml vial of clear glass Ph. Eur type III, with chlorobutyl rubber stopper type I.

2 g powder for solution for injection / infusion:

50 ml vial of clear glass Ph. Eur type I, with chlorobutyl rubber stopper type I.

Pack sizes:

20 ml vial of clear glass with chlorobutyl rubber stopper. Pack size: 10 x 1 g

50 ml vial of clear glass with chlorobutyl rubber stopper. Pack size: 10 x 2 g

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Electrolyte content: 1 g contains 2 mmol Na⁺, corresponding to 15 ml isotonic sodium chloride solution.

Aseptic technique should be used for reconstitution of the solution. The reconstituted solution should be administered immediately.

Depending upon the amount to be administered, there is recommended to use water for injection or sodium chloride solution 9 mg/ml to dissolve the powder.

Instructions for constitution of the solution for injection / infusion:

Amounts of solvent to be added for the preparation of a solution for injection/infusion are given in the table below:

Strength /vial	Method of administration			
	Short time intravenous infusion	Long time intravenous infusion	Intravenous Injection	Intra-muscular injection
1 g / 20 ml	-	-	20 ml	4 ml
2 g / 50 ml	100 ml ¹⁾	10 ml ²⁾	40 ml	-

1) The solution is prepared in Minibag plastic containers with use of transfer adapter, or in 100 ml bottle with use of transfer cannula.

2) 2 g is dissolved in 10 ml water for injection and mixed in suitable solution for infusion.

After reconstitution the solution should be clear. Do not use the solution if there are visible particles in the solution. Draw only one dose. Any unused solution should be discarded.

Cloxacillin is compatible with the following solutions for infusion:

- water for injection
- sodium chloride solution 9 mg/ml

Any unused product or waste 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]>

Module 3: Package Leaflet

PACKAGE LEAFLET:

INFORMATION FOR THE USER

Cloxacillin Stragen 1 g powder for solution for injection / infusion

Cloxacillin Stragen 2 g powder for solution for injection / infusion

Cloxacillin sodium corresponding to 1 g or 2 g cloxacillin

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Cloxacillin Stragen is and what it is used for
2. Before you use Cloxacillin Stragen
3. How to use Cloxacillin Stragen
4. Possible side effects
5. How to store Cloxacillin Stragen
6. Further information

1. WHAT CLOXACILLIN STRAGEN IS AND WHAT IT IS USED FOR

Cloxacillin Stragen is an antibiotic belonging to a class of drugs called penicillinase-resistant penicillines. Cloxacillin Stragen acts by inhibiting development of the bacteria's normal cell wall. Without cell wall, the bacteria are killed. Cloxacillin Stragen is active against Gram-positive aerobe and anaerobe bacteria, especially staphylococci.

Cloxacillin Stragen is used for treatment of infections with penicillinase producing staphylococci: skin and soft tissue infections, inflammation of the heart (endocarditis), inflammation of the bone marrow (osteomyelitis) and blood poisoning (sepsis).

2. BEFORE YOU USE CLOXACILLIN STRAGEN

Do not use Cloxacillin Stragen

- if you are allergic (hypersensitive) to cloxacillin
- if you are allergic (hypersensitive) to penicillines
- if you are allergic (hypersensitive) to cephalosporines.

Take special care with Cloxacillin Stragen

- if you have reduced kidney function.

Using other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

It is especially important to inform the doctor if you have been treated with:

- Probenecid (a drug for treatment of gout), since this may influence the excretion of cloxacillin.
- Oral contraceptives (the "Pill"), since penicillin's very rarely can reduce the absorption and hence the efficacy of the oral contraceptive.
- Methotrexate (a drug for the treatment of rheumatoid arthritis), since concomitant use of methotrexate can give increased efficacy/toxicity of methotrexate due to reduced excretion.
- Dicumarol products (drugs with a "blood-thinning" effect), since the efficacy of those can be reduced with concomitant treatment with cloxacillin.

Pregnancy and breast-feeding

Pregnancy: Long time clinical experience indicates little risk of adverse effects on pregnancy, foetus or the newborn child. Nevertheless, ask your doctor for advice if you are pregnant or plan to become pregnant.

Breast-feeding: The product is to a low extent excreted in breast milk. Effects on suckling children are not likely, even though the risk of influence on the intestine- and mouth flora in the child cannot be excluded. Small amounts of the active substance in the breast milk may cause increased risk of sensibilization. Ask your doctor for advice if you are breast-feeding.

Driving and using machines

This drug is not assumed to influence the ability to drive or to use machines.

3. HOW TO USE CLOXACILLIN STRAGEN

This is a medicinal product that is given to you by health care professional.

The product can be administered as intramuscular injection, as intravenous infusion. Infusion administration are used in cases where the patient is unable to take the drug orally as well as in cases where there is a need to treat the infection rapidly.

I.1.1.1.1

I.1.1.1.2 Dosage

I.1.1.1.3 The doctor adjusts the dosage individually for you.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cloxacillin Stragen can cause side effects, although not everybody gets them.

Common (occurs in more than 1 out of 100 users, but less than 1 out of 10):

Malaise, soft stool

Rash

Phlebitis (inflammation in a vein after intravenous injection)

Uncommon (occurs in more than 1 out of 1,000, but less than 1 out of 100 users):

Increased number of white blood cells of a special type (eosinophili) in blood.

Nettle fever (urticaria)

Rare (occurs in more than 1 out of 10,000, but less than 1 out of 1,000 users):

Decreased number of granulocytes cells (agranulocytosis) in blood.

Decreased number of white blood cells (leucopenia)

Acute inflammation of the colon (pseudomembraneous colitis)

Liver damage.

Kidney damage.

Severe allergic reactions (breathing difficulty or shock)

Local pain can occur with intramuscular injection.

Cloxacillin Stragen may cause a reduction in the number of white blood cells and your resistance to infections may be decreased. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CLOXACILLIN STRAGEN

Keep out of the reach and sight of children.

6. FURTHER INFORMATION

What Cloxacillin Stragen contains

- The active substance is cloxacillin sodium corresponding to 1 g or 2 g cloxacillin.
- The product contains no excipients.

What Cloxacillin Stragen looks like and contents of the pack

Cloxacillin Stragen is available as a powder for solution for injection / infusion. The powder is white to almost white. The powder is supplied as a single dose vial packed in a carton box. Each carton box contains 10 vials.

Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This leaflet was last approved in {MM/YYYY}.

<[To be completed nationally]>

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The following information is intended for medical or healthcare professionals only:

Electrolyte content: 1 g contains 2 mmol Na⁺, corresponding to 15 ml isotonic sodium chloride solution.

Preparation

Aseptic technique should be used for reconstitution of the solution.

Depending on the amount to be administered, it is recommended to use water for injection or sodium chloride solution 9 mg/ml to dissolve the powder.

Instruction for the preparation of the solution for injection/infusion:

The amount of solvent to be added for preparing of a solution for injection / infusion are given in table below:

Strength/ vial	Method of administration			
	Short time intravenous infusion	Long time intravenous infusion	Intravenous injection	Intra-muscular injection
1 g / 20 ml	-	-	20 ml	4 ml
2 g / 50 ml	100 ml ¹⁾	10 ml ²⁾	40 ml	-

1) The solution is prepared in Minibag plastic containers using a transfer adapter, or in 100 ml bottle using a transfer cannula.

2) 2 g is dissolved in 10 ml water for injection and mixed in appropriate solution for infusion.

Administration

After reconstitution the solution must be clear. Do not use the solution if there are visible particles in the solution. Draw up one dose only. Any unused solution should be discarded.

Incompatibility

Cloxacillin is compatible with intravenous infusion liquids:

- water for injection
- sodium chloride solution 9 mg/ml

This medicinal product must not be mixed with other medicinal products.

Stability

The chemical and physical in-use stability has been demonstrated for 6 hours at room temperature (25 °C) at room light and 24 hours at 2 – 8 °C protected from light.

From a microbiological point of view, the reconstituted solution should be used immediately. If reconstituted solution is not used immediately, then the storage time and storage conditions prior to use are the responsibility of the user and should normally not exceed 24 hours at 2 – 8 °C.

Unused product and waste should be disposed according to local requirements.

Module 4: Scientific discussion

This module reflects the scientific discussion for the approval of Cloxacillin Stragen 1g powder and solvent for solution for injection / infusion and Cloxacillin Stragen 2 g powder and solvent for solution for injection / infusion. The procedure was finalised at 28.06.06 (on Day 90). For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

Type of marketing authorisation, main features of disease/condition etc, discussion in CMD(h)

Based on review of the submitted data, the Member States have granted a marketing authorisation (MA) for Cloxacillin Stragen 1 g and 2 g, powder for solution for injection/infusion from Stragen Nordic AS. The first date of authorisation was on 10 November 2005 in Norway. The product is indicated for treatment of infections due to penicillinase producing staphylococci: Skin and soft tissue infections, endocarditis, abscesses, osteomyelitis and sepsis.

A comprehensive description of the indications and the posology is given in the SPC (see Module 3)

The marketing authorisation in Norway is granted according to Directive 2001/83/EC as amended, Article 10(1) generic application.

This concerns a generic application claiming essential similarity to the innovator product Ekvacillin. Ekvacillin (1 g, powder and solvent for solution for injection/infusion, 2 g, powder and solvent for solution for injection/infusion) has been registered in Norway by AstraZeneca since 01.01.1963, and 01.01.1967 respectively. In addition, reference is also made to Ekvacillin authorisations in the individual Member States (reference product). This type of application refers to information which is contained in the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the original authorised medicinal product, which is legally permitted once the data protection time of the dossier of the reference product and patent rights have expired. Usually, it is necessary to demonstrate that the generic product has the same pharmacokinetic profile as the originator. Since this product is an aqueous solution, a bioequivalence study is not necessary. No new pre-clinical and clinical studies were conducted, which is acceptable for this generic application.

II. QUALITY ASPECTS

II.1 Introduction

Pharmaceutical form, formulation, container system, etc

Cloxacillin Stragen is presented in the form of a powder for solution for injection/infusion 1 g and 2 g. The drug substance is added as cloxacillin sodium corresponding to 1 g and 2 g cloxacillin. No excipients have been used in the formulation. The powder for solution for injection/infusion is packed in vials made of colourless, transparent Ph. Eur. class III (20 ml) or class I (50 ml) glass.

II.2 2.2 Drug Substance

INN; chemical features like chemical class, chirality, manufacturing, specifications, stability

Cloxacillin sodium has a monograph in the Ph.Eur. and the manufacturer holds a Certificate of Suitability of the monograph. It is a white, crystalline powder which is freely soluble in water. The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are sufficiently described and validated. Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Pharmaceutical development, manufacture of the product, product specification, stability of the product

Cloxacillin powder for solution for injection/infusion 1 g and 2 g is formulated without excipients. No raw materials of human or animal origin are used in the product. The product development has taken the physico-chemical characteristics of the active substance into consideration.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC. No specific long term storage conditions are required. For in-use stability the chemical and physical in-use stability has been demonstrated for 6 hours at room temperature (25 °C) at room light and 24 hours at 2 °C to 8 °C protected from light.

III. NON-CLINICAL ASPECTS

Cloxacillin Stragen has been shown to be essentially similar to the approved product Ekvacillin «AstraZeneca AS». For this abridged application, non-clinical data have not been submitted and are not considered necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cloxacillin is a well-known active substance with established efficacy and tolerability.

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Ekvacillin, marketed by AstraZeneca AS.

This product is intended to be administered as an aqueous solution either intravenously or intramuscularly. It contains the same concentration of the same active substance (cloxacillin sodium) as the currently authorised product in Norway (Ekvacillin “AstraZeneca AS”). The test product (Cloxacillin Stragen “Stragen Nordic A/S”) and the reference product (Ekvacillin “AstraZeneca AS”) do not contain excipients. For the above-mentioned reasons a bioequivalence study is not necessary and there is no need for evaluation of clinical efficacy and safety issues.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cloxacillin Stragen 1 g and 2 g, powder and solvent for Solution for injection / infusion is a generic to Ekvacillin. Ekvacillin is a well-known medicinal product with an established efficacy and safety profile.

The product is an aqueous solution, and a bioequivalence study is not necessary. The SPC is consistent with that of the reference product.

Satisfactory chemical pharmaceutical documentation has been provided assuring consistent quality of the product.

The Member States mutually recognised the Norwegian evaluation and the marketing authorisation. There was no discussion in the CMD(h). Agreement between Member States was reached through a written procedure.

The following commitment was made by the applicant on Day 90 of the mutual recognition procedure:

- Results from user test of the Package Leaflet will be submitted as soon as possible.

Module 5: Update

Results from a user test of the Package Leaflet have been submitted to the Norwegian Medicines Agency. Any necessary amendments to the Package Leaflet resulting from the user test will be applied as a variation to the MA.

List of abbreviations

CMD (h)	Co-ordination Group for Mutual Recognition and Decentralised procedures (human)
ICH	International Conference of Harmonisation
MA	Marketing Authorisation
Ph.Eur.	European Pharmacopoeia
SPC	Summary of Product Characteristics