Summary of the Product Characteristics

hameln

Clindamycin-hameln 150 mg/ml Injection

1. NAME OF MEDICINAL PRODUCT

Clindamycin-hameln 150 mg/ml Injection

Active ingredient: clindamycin-2-dihydrogen phosphate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ampoule with 2 ml / 4 ml / 6 ml solution for injection contains 356.4 mg / 712.8 mg / 1069.2 mg clindamycin-2-dihydrogen phosphate corresponding to 300 mg / 600 mg / 900 mg of clindamycin.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute and chronic bacterial infections caused by pathogens susceptible to clindamycin, such as:

- Infections of the bones and joints
- Infections of the ear, nose and throat area
- Infections of the tooth and jaw area
- Infections of the lower respiratory tracts
- Infections of the pelvic and abdominal cavities
- Infections of the female genital organs
- Infections of the skin and soft tissue
- Scarlet fever
- Septicaemia
- Endocarditis

4.2 Posology and method of administration

Adults, and adolescents over 14 years receive:

- For moderately severe infections
  8 to 12 ml Clindamycin-hameln daily (equivalent to 1.2 to 1.8 g clindamycin),
- For severe infections
  16 to 18 ml Clindamycin-hameln daily (equivalent to 2.4 to 2.7 g clindamycin) in 2 to 4 divided doses.

The maximum daily dose for adults and adolescents over 14 years is 32 ml Clindamycin-hameln (equivalent to 4.8 g clindamycin) in 2 to 4 divided doses.

Children older than 4 weeks up to 14 years receive 20 to 40 mg/kg body weight clindamycin in 3 to 4 divided doses, the exact dose depending on the location and severity of the infection.

Dosage in the event of hepatic diseases:

In patients with hepatic disease of a moderate to severe degree, the elimination half-life of clindamycin is prolonged. A reduction in dosage is generally not necessary if Clindamycin-hameln is administered every 8 hours. However, the plasma concentration of clindamycin should be monitored in patients with severe hepatic insufficiency. Depending on the results, this measure can make a reduction in dosage or an increase in the dose intervals necessary.

Dosage in the event of renal diseases

In the event of renal diseases, the elimination half-life is prolonged; however, a dosage reduction is unnecessary in the event of mild to moderate impairment of renal function. Nevertheless, the plasma concentration should be monitored in patients with severe renal insufficiency or anuria. Depending on the results, this measure can make a reduction in dosage or an increase in the dose interval of 8 or even 12 hours necessary.

Dosage in the event of haemodialysis

Clindamycin cannot be removed by haemodialysis. Thus, an additional dose either before or after dialysis is unnecessary.

Clindamycin-hameln is injected intramuscularly or infused intravenously.

Under no circumstances may Clindamycin-hameln be administered undiluted as an intravenous injection!

A single dose of clindamycin for intramuscular application should not exceed 600 mg.

Before intravenous infusion, the solution must be diluted until the concentration is no greater than 12 mg clindamycin per ml solution. The infusion rate should not exceed 30 mg clindamycin per minute. No more than 1200 mg clindamycin should be administered per hour as a single infusion.

4.3 Contraindications

Clindamycin-hameln may not be used in patients allergic to clindamycin or lincomycin (parallergy exists).

Clindamycin-hameln may not be administered to patients with an allergy to benzyl alcohol or local anaesthetics (such as lidocaine or drugs related to lidocaine).

Clindamycin-hameln may not be used in neonates (particularly to immature premature babies) due to the content of benzyl alcohol.

4.4 Special warnings and precautions for use

Care must be taken in the following cases:

- Restricted hepatic function,
- Impaired neuromuscular transfer (myasthenia gravis, Parkinson's disease) and
- History of gastrointestinal ailments (e.g., previous inflammation of the large intestine)

Benzyl alcohol may cause toxic reactions and anaphylactic reactions in infants and children up to 3 years old.

In long-term therapy (treatment for longer than 3 weeks), the haemogram as well as hepatic and renal function should be checked at regular intervals.

Long-term and repeated application of Clindamycin-hameln can lead to a superinfection and/or colonisation with resistant pathogens or yeasts on the skin and mucous membranes.

Under certain circumstances, clindamycin therapy may be an alternative form of treatment in patients with a penicillin allergy (penicillin hypersensitivity). There have been no reports of a cross-allergy between clindamycin and penicillin and, based on the structural differences between the substances, this is not to be expected. However, in individual cases, information does exist on anaphylaxis (hypersensitivity) towards clindamycin in persons with whom a penicillin allergy already exists. This should be taken into consideration in a course of clindamycin treatment in patients with a penicillin allergy.

Severe acute allergic reactions occur very rarely (e.g. anaphylactic shock).

At this point, treatment with Clindamycin-hameln has to be stopped immediately and adequate emergency response needs to be conducted (e.g. antihistamine, corticosteroid, sympathicomimeticum and if applicable artificial respiration).

Therapy of pseudomembranous enterocolitis

Depending on the indication, consideration should be given to discontinuing therapy and possibly implementing appropriate treatment immediately (e.g. application of special antibiotics / chemotherapeutic agents, whose efficacy has been demonstrated clinically). Drugs that inhibit peristalsis are contraindicated.

Clindamycin-hameln may not be used during acute infections of the respiratory tract if caused by a viral infection.

Clindamycin-hameln is not intended to be used for treatment of meningitis as the concentrations of antibodies in the cerebrospinal fluid are insufficient.

This medicinal product contains **11.8 mmol (272 mg)** sodium chloride per max. daily dose (32 ml Clindamycin-hameln). To be taken into consideration by patients on a controlled sodium (low sodium) diet.

4.5 Interaction with other medicinal products and other forms of interaction

Clindamycin-hameln should not be combined with erythromycin, as an antagonistic effect has been observed in vitro, as far as the antibacterial effect is concerned.

Cross-resistance of the pathogens between clindamycin and lincomycin exists.

On account of its neuromuscular-blocking properties, Clindamycin-hameln may enhance the effect of muscle relaxants (e.g., ether, tubocurarine, pancuronium halides). As a result, unexpected, life-threatening situations may arise during operations.

There is a question mark over the reliability of oral contraceptives ("the pill") when taken simultaneously with Clindamycin-hameln. For this reason, other contraceptive measures should be taken in addition during treatment with Clindamycin-hameln.

4.6 Pregnancy and lactation

Use during pregnancy and lactation requires careful weighing up of the benefits and risks. To date, observations in humans have failed to produce evidence of embryotoxic effects.

Sensitisation, diarrhoea and blastomyces colonization of the mucous membranes in breast-fed infants cannot be ruled out.

4.7 Effects on ability to drive and use machines

Clindamyin has a minor or moderate influence to ability to drive and use machines.

4.8 Undesirable effects

The frequency of the adverse reactions are listed according to the following convention:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1000 to <1/100)
Rare	(≥1/10000 to <1/1000)
Very Rare	(<1/10000)
Not known	(cannot be estimated from the available data)

Commonly (≥1%-<10%) to very commonly (≥10%), loose stool and diarrhoea occur sometimes together with nausea, vomiting, stomach pains. These are mainly of a mild nature and often subside during or otherwise after discontinuing therapy. These adverse reactions are dependent on the application and the dosage. Oesophagitis and inflammation of the oral mucous membranes are also possible

In very rare cases (<0.01%), pseudomembranous enterocolitis may develop under Clindamycin-hameln therapy (refer to Emergency measures, symptoms and antidotes).

Commonly (≥1%-<10%): Local irritations, pain, indurations and sterile abscesses manifest at the injection site following intramuscular injection.

Intravenous application is commonly (≥1%-<10%) followed by pain and thrombophlebitis. Following rapid intravenous injection, hypersensitive reactions may occur in the form of flushing, feeling of nausea or, uncommonly (≥0.1%-<1%), serious cardiovascular disorders (e.g., decrease in blood pressure and cardiac arrest). Clindamycin-hameln must therefore not be injected intravenously, but be applied in the form of an infusion. For this, Clindamycin-hameln must be diluted beforehand.

Uncommonly, (≥0.1%-<1%) allergies in the form of morbilliform exanthema as well as pruritus and urticaria are observed. Very rare (≥0.01%-<0.1%) are swellings (Quincke's oedema and articular swelling), drug fever as well as erythema exudativum multiforme (e.g., Stevens-Johnson syndrome) and Lyell's syndrome. The occurrence of an anaphylactic shock is very rare (<0.01%). This reaction may occur after the first treatment.

Uncommon (≥0.1%-<1%) and reversible are effects on the haemogram, which may be of an allergic and toxic nature and be expressed in the form of thrombocytopenia, leucopenia, eosinophilia, neutropenia and granulocytopenia.

Mild, transient elevation of the serum transaminases occur uncommonly (≥0.1%-<1%) to commonly (≥1%-<10%). Very rarely (<0.01%), transient hepatitis with cholestatic jaundice is observed.

A neuromuscular-blocking effect is uncommon (≥0.1%-<1%).

Rare (≥0.01%-<0.01%) are itching, colpitis as well as desquamatous and bullous cutaneous inflammation.

Polyarthritis may be observed very rarely (<0.01%).

4.9 Overdose

No overdose symptoms have yet been observed. Haemodialysis and peritoneal dialysis are ineffective. There is no known specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacological properties

Clindamycin is a semi-synthetic derivative of lincomycin. It belongs to the lincosamides group, which as pyranosides are not related to any hitherto known antibiotics. Clindamycin is primarily bacteriostatic and, to an extent depending on the concentration at the location of the infection and the susceptibility of the pathogens, it is bactericidal.

The development of secondary resistance is rare.

Complete cross resistance of pathogens exists between clindamycin and lincomycin and partial cross resistance of pathogens between clindamycin and erythromycin.

Breakpoints

The MIC breakpoints for clindamycin in accordance with DIN 58940 are:

Susceptible: ≤1 mg/l

Intermediate: 2-4 mg/l

Resistant: >8 mg/l

Susceptibility

The prevalence of acquired resistance may vary geographically and in the course of time for selected species, which is why local information on resistance is desirable, particularly when treating severe infections.

The following table only allows judgement on the probability of an organism being susceptible to the drug or not.

The prevalence of microbial resistance to clindamycin:

- * denotes data from Germany,
- without asterisk = data from European countries.

Where no resistance percentage is indicated, the MIC values suggest susceptible or resistant strains according to the listing.

Species	Resistant %
Susceptible	
Gram-positive aerobes	
Listeria monocytogenes	
Staphylococcus aureus	6.9 - 10.1*
Staphylococcus epidermidis	34.8 - 39.7
Staphylococcus haemolyticus	18.9* - 40.0*
Stapyhlococcus hominis	22.2
Staphylococcus saprophyticus	1.4
Streptococcus pneumoniae PEN-S Streptococcus pneumoniae PEN-I Streptococcus pneumoniae PEN-R	0 - 4.3 3 - 23 6.7 - 46.5
Streptococci alpha- and nonhemolytic	0 - 12.2
beta-hemolytic group A Streptococci	0 - 4.3
betahemolytic group B, C and G Streptococci	4.6
Anaerobes	
Clostridium spp.	
Peptostreptococcus spp.	
Porphyromonas gingivalis	
Prevotella spp.	
Intermediate	
Gram-positive aerobes	
Staphylococcus aureus MET-R	52.3 - 89.1
Staphylococcus epidermidis MET-R	53.7 - 54.1
Staphylococcus haemolyticus MET-R	42.2*
Anaerobes	
Bacteroides caccae	
Bacteroides distasonis	
Bacteroides fragilis	2.5 - 49
Bacteroides thetaiotaomicron	
Bacteroides vulgatus	
Fusobacterium spp.	
Resistant	
Gram-positive aerobes	
Corynebacterium jeikeium	
Enterococcus faecalis	
Enterococcus faecium	

PEN-S, PEN-I, PEN-R: Penicillin-sensitive, -intermediate resistant, and -resistant respectively

MET-R: Methicillin-resistant

* Up to 50% of methicillin-susceptible S. aureus have been reported to be resistant to clindamycin in some areas. More than 90% of methicillin-resistant S. aureus (MRSA) are resistant to clindamycin and clindamycin should not be used in the event of any suspicion of MRSA.

5.2 Pharmacokinetic properties

A distinction need only be drawn between the clindamycin derivatives employed until the absorption and cleavage of the esters occur. Thereafter, clindamycin is present in the organism as a free base (effective form). The esters are to be regarded as pro-drugs.

Clindamycin-2-dihydrogen phosphate is a water-soluble ester for parenteral application. The maximum serum level 3 hours after intramuscular injection of 300 mg is 6 µg/ml. The mean serum concentration 1 hour after intravenous application of 300 mg is 4 to 6 µg/ml.

The extent to which clindamycin binds to plasma proteins depends on the concentration and lies between 60% and 94% in the therapeutic range.

Clindamycin passes tissue readily, crosses the placenta barrier and transfers into the mother's milk. Diffusion into the liquor space is inadequate even when the meninges are inflamed. High concentrations are attained in bone tissue.

Clindamycin is primarily degraded in the liver. Some metabolites are microbiologically active. Medicines that function as enzyme inductors in the liver shorten the mean dwell time of clindamycin in the body.

Roughly two thirds of clindamycin is eliminated with the faeces and one third with the urine.

The serum half-life of clindamycin is roughly 3 hours in adults and roughly 2 hours in children. The half-life is prolonged in patients with restricted renal function and moderate to severe hepatic insufficiency.

Clindamycin is not dialyzable.

5.3 Preclinical safety data

a) Acute toxicity

Studies of the acute toxicity of clindamycin and its salts on various animal species have produced LD_{50} values ranging from 1800 to 2620 mg/kg for oral intake and between 245 and 820 mg/kg for intravenous administration. The symptoms of intoxication are a very pronounced reduction in activity of the animals and convulsions.

b) Chronic toxicity

Repeated administration of clindamycin phosphate to rats for 6 days (subcutaneous application) and dogs (intravenous and intramuscular application) did not cause systemic toxic effects. Application of clindamycin phosphate for 1 month to rats (s.c.) and dogs (i.m. and i.v.) also failed to produce any substance-induced influences on body weight development, clinico-chemical and haematological parameters or on organ histopathology. In dogs, daily intramuscular administration of 30 to 90 mg/kg led to increases in SGOT and SGPT as well as a slight dose-dependent rise in the relative liver weight, without indications of morphological changes.

Local reactions at the injection site (inflammation, haemorrhagiae and tissue damage) were observed in intramuscular and subcutaneous application, although the concentration of the applied solution far exceeded the maximum permissible therapeutic concentration.

c) Mutagenic and tumourigenic potential

In vitro and in vivo studies of the mutagenicity of clindamycin have failed to produce indications of a mutagenic potential. No long-term studies of the tumourigenic potential of clindamycin have been performed on animals.

d) Reproduction toxicity

Studies performed with clindamycin on rats and mice failed to produce indications of impaired fertility or embryo-foetotoxic properties. A large study on pregnant women in which roughly 650 neonates exposed during the first trimester of pregnancy were examined, did not show a higher incidence of malformations.

The concentration of clindamycin in umbilical cord blood was found to be roughly 50% of the maternal serum concentration. It is to be assumed that therapeutic concentrations can be reached in the foetus. Transfer into mother's milk has been demonstrated; the concentrations were as much as 4 µg/ml after maternal doses of 600 mg and as much as 2 µg/ml after doses of 300 mg. With the exception of an isolated case history, so far there has not been any indication of adverse effects on breast-fed infants.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains 18 mg / 36 mg / 54 mg benzyl alcohol per 2 ml / 4 ml / 6 ml, sodium edetate, sodium hydroxide (for pH adjustment) and water for injections.

6.2 Incompatibilities

Clindamycin-hameln may not be administered in a mixed injection along with ampicillin, phenytoin sodium, barbiturates, aminophylline, calcium gluconate or magnesium sulphate. These drugs must always be administered separately.

6.3 Shelf life

The shelf life is 2 years.

Do not use the medicine after the expiry date.

After dilution, chemical and physical in-use stability has been demonstrated for 48 hours at 20°C-25°C.

From a microbiological point of view, once diluted, the product 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 dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.

Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

Package with 5 or 10 ampoules containing 2, 4 or 6 ml solution for injection.

Possibly, not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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7. MARKETING AUTHORISATION HOLDER

hameln pharmaceuticals gmbh
Langes Feld 13, 31789 Hameln

Marketed by
hameln pharma plus gmbh
Langes Feld 13, 31789 Hameln

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Oktober 2008

11. DOSIMETRY

Prescription only medicine (POM)