Package leaflet: Information for the patient

Daptomycin Noridem 350 mg Powder for solution for injection/infusion
Daptomycin Noridem 500 mg Powder for solution for injection/infusion

daptomycin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Daptomycin Noridem is and what it is used for
2. What you need to know before you are given Daptomycin Noridem
3. How Daptomycin Noridem is given
4. Possible side effects
5. How to store Daptomycin Noridem
6. Contents of the pack and other information

The name of your medicine is **Daptomycin Noridem 350 mg & 500 mg Powder for solution for injection/infusion**. In the rest of this leaflet the name of the medicine shall be Daptomycin Noridem.

1. What Daptomycin Noridem is and what it is used for

The active substance in Daptomycin Noridem is daptomycin. Daptomycin is an antibacterial that can stop the growth of certain bacteria. Daptomycin Noridem is used in adults and in children and adolescents (age from 1 to 17 years) to treat infections of the skin and the tissues below the skin.
It is also used to treat infections in the blood when associated with skin infection.
Daptomycin Noridem is also used in adults to treat infections in the tissues that line the inside of the heart (including heart valves) which are caused by a type of bacteria called *Staphylococcus aureus*. It is also used to treat infections in the blood caused by the same type of bacteria when associated with heart infection.
Depending on the type of infection(s) that you have, your doctor may also prescribe other antibacterials while you are receiving treatment with Daptomycin Noridem.

2. What you need to know before you are given Daptomycin Noridem

You should not be given Daptomycin Noridem
- if you are allergic to daptomycin or any of the other ingredients of this medicine (listed in section 6).

If this applies to you, tell your doctor or nurse. If you think you may be allergic, ask your doctor or nurse for advice.

Warnings and precautions
Talk to your doctor or nurse before you are given Daptomycin Noridem
- If you have, or have previously had kidney problems. Your doctor may need to change the dose of Daptomycin Noridem (see section 3 of this leaflet).
- Occasionally, patients receiving daptomycin may develop tender or aching muscles or muscle weakness (see section 4 of this leaflet for more information). If this happens tell your doctor. Your doctor will make sure you have a blood test and will advise whether or not to continue with Daptomycin Noridem. The symptoms generally go away within a few days of stopping daptomycin.
- If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores, or serious kidney problems after taking daptomycin.
- If you are very overweight. There is a possibility that your blood levels of daptomycin could be higher than those found in persons of average weight and you may need careful monitoring in case of side effects.

If any of these applies to you, tell your doctor or nurse before you are given Daptomycin Noridem.

Tell your doctor or nurse straight away if you develop any of the following symptoms:
- Serious, acute allergic reactions have been observed in patients treated with nearly all antibacterial agents, including daptomycin. The symptoms can include wheezing, difficulty breathing, swelling of the face, neck and throat, rashes and hives, or fever.
- Serious skin disorders have been reported with the use of Daptomycin Noridem. The symptoms that occur with these skin disorders can include:
  - a new or worsening fever,
  - red raised or fluid-filled skin spots which may start in your armpits or on your chest or groin areas and which can spread over a large area of your body,
  - blisters or sores in your mouth or on your genitals.
- A serious kidney problem has been reported with the use of Daptomycin Noridem. The symptoms can include fever and rash
- Any unusual tingling or numbness of the hands or feet, loss of feeling or difficulties with movements. If this happens, tell your doctor who will decide whether you should continue the treatment.
- Diarrhoea, especially if you notice blood or mucus, or if diarrhoea becomes severe or persistent.
- New or worsening fever, cough or difficulty breathing. These may be signs of a rare but serious lung disorder called eosinophilic pneumonia. Your doctor will check the condition of your lungs and decide whether or not you should continue Daptomycin Noridem treatment.

Daptomycin Noridem may interfere with laboratory tests that measure how well your blood is clotting. The results can suggest poor blood clotting when, in fact, there is no problem. Therefore it is important that your doctor takes into account that you are receiving Daptomycin Noridem. Please inform your doctor that you are on treatment with Daptomycin Noridem.

Your doctor will perform blood tests to monitor the health of your muscles both before you start treatment and frequently during treatment with Daptomycin Noridem.

Children and adolescents
Daptomycin Noridem should not be administered to children below one year of age as studies in animals have indicated that this age group may experience severe side effects.

Use in elderly
People over the age of 65 can be given the same dose as other adults, provided their kidneys are working well.

Other medicines and Daptomycin Noridem
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. It is particularly important that you mention the following:
- Medicines called statins or fibrates (to lower cholesterol) or ciclosporin (a medicinal product used in transplantation to prevent organ rejection or for other conditions, e.g. rheumatoid arthritis or atopic dermatitis). It is possible that the risk of side effects affecting the muscles may be higher when any of these medicines (and some others that can affect muscles) is taken during treatment with Daptomycin Noridem. Your doctor may decide not to give you Daptomycin Noridem or to stop the other medicine for a while.
- Pain killing medicines called non-steroidal anti-inflammatory drugs (NSAIDs) or COX-2 inhibitors (e.g. celecoxib). These could interfere with the effects of Daptomycin Noridem in the kidney.
- Oral anti-coagulants (e.g. warfarin), which are medicines that prevent blood from clotting. It may be necessary for your doctor to monitor your blood clotting times.

Pregnancy and breast-feeding
Daptomycin Noridem is not usually given to pregnant women. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine.
Do not breast-feed if you are receiving Daptomycin Noridem, because it may pass into your breast milk and could affect the baby.

Driving and using machines
Daptomycin Noridem has no known effects on the ability to drive or use machines.

Daptomycin Noridem contains sodium
This medicine contains less than 1 mmol sodium
(23 mg) per vial, that is to say essentially 'sodium-free'.

3. How Daptomycin Noridem is given

Daptomycin Noridem will usually be given to you by a doctor or a nurse.

Adults (18 years of age and above)
The dose will depend on how much you weigh and the type of infection being treated. The usual dose for adults is 4 mg for every kilogram (kg) of body weight once daily for skin infections or 6 mg for every kg of body weight once daily for a heart infection or a blood infection associated with skin or heart infection. In adult patients, this dose is given directly into your blood stream (into a vein), either as an infusion lasting about 30 minutes or as an injection lasting about 2 minutes.
The same dose is recommended in people aged over 65 years provided their kidneys are working well.
If your kidneys do not work well, you may receive Daptomycin Noridem less often, e.g. once every other day. If you are receiving dialysis, and your next dose of Daptomycin Noridem is due on a dialysis day, you will be usually given Daptomycin Noridem after the dialysis session.

The following information is intended for healthcare professionals only:

Important: Please refer to the Summary of Product Characteristics before prescribing.

Instructions for use and handling

In adults, daptomycin may be administered intravenously as an infusion over 30 or 60 minutes or as an injection over 2 minutes. Unlike in adults, daptomycin should not be administered by injection over a 2 minute period in paediatric patients. Paediatric patients 7 to 17 years old should receive daptomycin infused over 30 minutes. In paediatric patients under 7 years old receiving a 9-12 mg/kg dose, daptomycin should be administered over 60 minutes. Preparation of the solution for infusion requires an additional dilution step as detailed below.

Daptomycin Noridem given as an intravenous infusion over 30 or 60 minutes

350 mg presentation:
A 50 mg/mL concentration of Daptomycin Noridem for infusion can be achieved by reconstituting the lyophilised product with 7 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.

500 mg presentation:
A 50 mg/mL concentration of Daptomycin Noridem for infusion can be achieved by reconstituting the lyophilised product with 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.

The lyophilised product takes approximately 5 minutes to dissolve. The fully reconstituted product will appear clear and may have a few small bubbles or foam around the edge of the vial.

To prepare Daptomycin Noridem for intravenous infusion, please adhere to the following instructions:
Aseptic technique should be used throughout to reconstitute or dilute lyophilised Daptomycin Noridem.

For Reconstitution:
1. The plastic flip off cap should be removed to expose the central portions of the rubber stopper. Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any other surface.
   - For **Daptomycin Noridem 350 mg Powder for solution for injection / infusion** draw 7 mL of sodium chloride 9 mg/mL (0.9%) solution for injection into a syringe using a sterile transfer needle, that is 21 gauge or smaller in diameter, or a needleless device, then slowly inject through the center of the rubber stopper into the vial pointing the needle towards the wall of the vial.
   - For **Daptomycin Noridem 500 mg Powder for solution for injection / infusion** draw 10mL of sodium chloride 9 mg/mL (0.9%) solution for injection into a syringe using a sterile transfer needle, that is 21 gauge or smaller in diameter, or a needleless device, then slowly inject through the center of the rubber stopper into the vial pointing the needle towards the wall of the vial.
2. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes.
3. Finally the vial should be gently rotated/ swirled for a few minutes as needed to obtain a clear reconstituted solution. Vigorous shaking/agitation should be avoided to prevent foaming of the product.
4. The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspected for the absence of particulates prior to use. Reconstituted solutions of Daptomycin Noridem range in colour from pale yellow to light brown.
5. The reconstituted solution should then be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection (typical volume 50 mL).

For Dilution:
1. Slowly remove the appropriate reconstituted liquid (50 mg daptomycin/mL) from the vial using a new sterile needle that is 21 gauge or smaller in diameter.
2. By inverting the vial in order to allow the solution to drain towards the stopper. Using a new syringe, insert the needle into the inverted vial. Keeping the vial inverted, position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove the required solution from the inverted vial.
3. Expel air, large bubbles, and any excess solution in order to obtain the required dose.
4. Transfer the required reconstituted dose into 50 mL sodium chloride 9 mg/mL (0.9%) solution for injection.
5. The reconstituted and diluted solution should then be infused intravenously over 30 or 60 minutes.

Daptomycin Noridem is not physically or chemically compatible with glucose-containing solutions. The following have been shown to be compatible when added to Daptomycin Noridem containing infusion solutions: aztreonam, ceftazidime, ceftriaxone, gentamicin, fluconazole, levofloxacin, dopamine, heparin and lidocaine.

After reconstitution:
Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for 12 hours at 25°C and up to 48 hours at 2°C – 8°C.

After dilution:
Chemical and physical in-use stability of the diluted solution in infusion bags is established for 12 hours at 25°C or 24 hours at 2°C – 8°C.

For the 30-minute intravenous infusion, the combined storage time (reconstituted solution in vial and diluted solution in infusion bag) at 25°C must not exceed 12 hours (24 hours if refrigerated).

For the 2-minute intravenous injection, the storage time of the reconstituted solution in the vial at 25°C must not exceed 12 hours (or 48 hours at 2°C – 8°C).

However, from a microbiological point of view the product should be used immediately. No preservative or bacteriostatic agent is present in this product. 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 – 8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Children and adolescents (1 to 17 years of age)
The dose for children and adolescents (1 to 17 years of age) will depend on the age of patient and the type of infection being treated. This dose is given directly into the blood stream (into a vein), as an infusion lasting about 30-60 minutes.

A course of treatment usually lasts for 1 to 2 weeks for skin infections. For blood or heart infections and skin infections your doctor will decide how long you should be treated.

Detailed instructions for use and handling are given at the end of the leaflet.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most serious side effects are described below:
Serious side effects with frequency not known (frequency cannot be estimated from the available data)

- A hypersensitivity reaction (serious allergic reaction including anaphylaxis and angioedema) has been reported, in some cases during administration of daptomycin. This serious allergic reaction needs immediate medical attention. Tell your doctor or nurse straight away if you experience any of the following symptoms:
  - Chest pain or tightness,
  - Rash or hives,
  - Swelling around throat,
  - Rapid or weak pulse,
  - Wheezing,
  - Fever,
  - Shivering or trembling,
  - Hot flushes,
  - Dizziness,
  - Fainting,
  - Metallic taste.

Tell your doctor straight away if you experience unexplained muscle pain, tenderness, or weakness. Muscle problems can be serious, including muscle breakdown (rhabdomyolysis), which can result in kidney damage.

Other serious side effects that have been reported with the use of daptomycin are:
- A rare but potentially serious lung disorder called eosinophilic pneumonia mostly after more than 2 weeks of treatment. The symptoms can include difficulty breathing, new or worsening cough, or new or worsening fever.
- Serious skin disorders. The symptoms can include:
  - a new or worsening fever,
  - red raised or fluid-filled skin spots which may start in your armpits or on your chest or groin areas and which can spread over a large area of your body,
  - blisters or sores in your mouth or on your genitals.
- A serious kidney problem. The symptoms can include fever and rash.

If you experience these symptoms, tell your doctor or nurse straight away. Your doctor will perform additional tests to make a diagnosis.

The most frequently reported side effects are described below:

Common side effects (may affect up to 1 in 10 people)
- Fungal infections such as thrush,
- Urinary tract infection,
- Decreased number of red blood cells (anaemia),
- Dizziness, anxiety, difficulty in sleeping,
- Headache,
- Fever, weakness (asthenia),
- High or low blood pressure,
- Constipation, abdominal pain,
- Diarrhoea, feeling sick (nausea) or being sick (vomiting),
- Flatulence,
- Abdominal swelling or bloating,
- Skin rash or itching,
- Pain, itchiness or redness at the site of infusion,
- Pain in arms or legs,
- Blood testing showing higher levels of liver enzymes or creatine phosphokinase (CPK).

Other side effects which may occur following daptomycin treatment are described below:

Uncommon side effects (may affect up to 1 in 100 people)
- Blood disorders (e.g increased number of small blood particles called platelets, which may increase the tendency for blood clotting, or higher levels of certain types of white blood cells),
- Decreased appetite,
- Tingling or numbness of the hands or feet, taste disturbance,
- Trembling,
- Changes in heart rhythm, flushes,
- Indigestion (dyspepsia), inflammation of the tongue,
- Itchy rash of skin,
- Muscle pain, cramping or weakness, inflammation of the muscles (myositis), joint pain,
- Kidney problems,
- Inflammation and irritation of the vagina,
- General pain or weakness, tiredness (fatigue),
- Blood test showing increased levels of blood sugar, serum creatinine, myoglobin, or lactate dehydrogenase (LDH), prolonged blood clotting time or imbalance of salts,
- Itchy eyes.

Rare side effects (may affect up to 1 in 1,000 people)
- Yellowing of the skin and eyes,
- Prothrombin time prolonged.

Frequency not known (frequency cannot be estimated from the available data)
Antibacterial-associated colitis, including pseudomembranous colitis (severe or persistent diarrhoea containing blood and/ or mucus, associated with abdominal pain or fever), easy bruising, bleeding gums, or nosebleeds.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Daptomycin Noridem

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and label after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

<u>After reconstitution:</u>
Chemical and physical in-use stability of the reconstituted solution in the vial has been demonstrated for 12 hours at 25°C and up to 48 hours at 2°C – 8°C.

<u>After dilution:</u>
Chemical and physical in-use stability of the diluted solution in infusion bags is established for 12 hours at 25°C or 24 hours at 2°C – 8°C.

For the 30-minute intravenous infusion, the combined storage time (reconstituted solution in vial and diluted solution in infusion bag) at 25°C must not exceed 12 hours (or 24 hours at 2°C – 8°C).

For the 2-minute intravenous injection, the storage time of the reconstituted solution in the vial at 25°C must not exceed 12 hours (or 48 hours at 2°C – 8°C).
However, from a microbiological point of view the product should be used immediately. No preservative or bacteriostatic agent is present in this product. 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 – 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

<u>After admixture:</u>
Chemical and physical in-use stability of the admixtures is established for 2 hours at 25°C.
Do not use this medicine if you notice any signs of humidity or if the reconstitution solution is not clear and/or has particles in it.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Daptomycin Noridem contains
- The active substance is daptomycin.

One vial of powder contains 350 mg or 500 mg daptomycin.
- The other ingredient is sodium hydroxide.

What Daptomycin Noridem looks like and contents of the pack
Daptomycin Noridem is supplied as a pale yellow to light brown cake or powder in a glass vial. It should be mixed with a solvent to form a liquid before it is administered.

Daptomycin Noridem is available in packs containing 1, 5, 10 or 50 vials.
Not all pack sizes may be marketed.

Marketing Authorization Holder and Manufacturer

Marketing Authorization Holder: Noridem Enterprises Limited, Evagorou & Makariou, Mitsi Building 3, Office 115, 1065 Nicosia, Cyprus.

Manufacturer: DEMO S.A. PHARMACEUTICAL INDUSTRY, 21st Km National Road Athens–Lamia, 14568 Krioneri, Attiki, Greece,

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<u>After admixture:</u>
Chemical and physical in-use stability of the admixtures is established for 2 hours at 25°C.

Daptomycin Noridem given as 2-minute intravenous injection (adult patients only)

Water should not be used for reconstitution of Daptomycin Noridem for intravenous injection. Daptomycin Noridem should only be reconstituted with sodium chloride 9 mg/mL (0.9%) solution for injection.

<u>350 mg presentation:</u>
A 50 mg/mL concentration of Daptomycin Noridem for injection is obtained by reconstituting the lyophilised product with 7 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.

<u>500 mg presentation:</u>
A 50 mg/mL concentration of Daptomycin Noridem for injection is obtained by reconstituting the lyophilised product with 10mL of sodium chloride 9 mg/mL (0.9%) solution for injection.

The lyophilised product takes approximately 5 minutes to dissolve. The fully reconstituted product will appear clear and may have a few small bubbles or foam around the edge of the vial.

To prepare Daptomycin Noridem for intravenous injection, please adhere to the following instructions:
Aseptic technique should be used throughout to reconstitute lyophilised Daptomycin Noridem.

1. The plastic flip off cap should be removed to expose the central portions of the rubber stopper. Wipe the top of the rubber stopper with an alcohol swab or other antiseptic solution and allow to dry. After cleaning, do not touch the rubber stopper or allow it to touch any other surface.
   - For **Daptomycin Noridem 350 mg Powder for solution for injection / infusion** draw 7 mL of sodium chloride 9 mg/mL (0.9%) solution for injection into a syringe using a sterile transfer needle, that is 21 gauge or smaller in diameter, or a needleless device, then slowly inject through the center of the rubber stopper into the vial pointing the needle towards the wall of the vial.
   - For **Daptomycin Noridem 500 mg Powder for solution for injection / infusion** draw 10mL of sodium chloride 9 mg/mL (0.9%) solution for injection into a syringe using a sterile transfer needle, that is 21 gauge or smaller in diameter, or a needleless device, then slowly inject through the center of the rubber stopper into the vial pointing the needle towards the wall of the vial.
2. The vial should be gently rotated to ensure complete wetting of the product and then allowed to stand for 10 minutes.
3. Finally the vial should be gently rotated/ swirled for a few minutes as needed to obtain a clear reconstituted solution. Vigorous shaking/agitation should be avoided to prevent foaming of the product.
4. The reconstituted solution should be checked carefully to ensure that the product is in solution and visually inspected for the absence of particulates prior to use. Reconstituted solutions of Daptomycin Noridem range in colour from pale yellow to light brown.
5. Slowly remove the reconstituted liquid (50 mg daptomycin / mL) from the vial using a sterile needle that is 21 gauge or smaller in diameter.
6. Invert the vial in order to allow the solution to drain towards the stopper. Using a new syringe, insert the needle into the inverted vial. Keeping the vial inverted, position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel in order to remove all of the solution from the inverted vial.
7. Replace needle with a new needle for the intravenous injection.
8. Expel air, large bubbles, and any excess solution in order to obtain the required dose.
9. The reconstituted solution should then be injected intravenously slowly over 2 minutes.

Chemical and physical in-use stability on the reconstituted solution in the vial has been demonstrated for 12 hours at 25°C and up to 48 hours if stored under refrigeration (2°C – 8°C).

However, from a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C unless reconstitution /dilution has taken place in controlled and validated aseptic conditions.

This medicinal product must not be mixed with other medicinal products except those mentioned above.

Daptomycin Noridem vials are for single-use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.