YANOVEN®

2 g + 0.25 g sterile powder and solvent for I.M. injectable solution

4 g + 0.5 g sterile powder for solution for I.V. infusion

Piperacillin + Tazobactam

Pharmacotherapeutic group
Antibacterials for systemic use. Combination of penicillins with beta-lactamase inhibitors.

Therapeutic indications
Yanoven is indicated for the treatment of the following infections with proven or suspected presence of susceptible microorganisms: Infections of the lower respiratory tract, infections of the urinary tract (complicated and not), intra-abdominal infections, skin infections, bacterial septicemia, polymicrobial infections. **Yanoven** is indicated for the treatment of mixed bacterial infections including those assumed to be caused by aerobic and anaerobic microorganisms (intra-abdominal, skin, lower respiratory tract). Although **Yanoven** is indicated only for the specific conditions indicated above, it may also be used for any infections caused by piperacillin-susceptible bacteria without requiring the addition of other antibiotics in presence of β-lactamase producing organisms.
Yanoven is especially useful in the treatment of mixed infections and, because of its wide spectrum of activity, can adequately cover the patient during presumptive therapy while waiting for susceptibility results.
In particular it is indicated for the presumptive monotherapy of infections in adult patients with febrile neutropenia; anyhow, the treatment must be adjusted in function of culture and bacteriological results.
Yanoven acts synergically with aminoglycosides against several strains of *Pseudomonas aeruginosa*. This combination, that involves the administration of drugs at full dosage, is effective, especially in immunodepressed patients; anyhow, the treatment must be adjusted in function of culture and bacteriological results.
Children aged under 12
In hospitalized children aged between 2 and 12, **Yanoven** is indicated for the treatment of intra-abdominal infections, including appendicitis complicated by rupture or abscess, peritonitis and biliary tract infections. The use of the drug for this indication in children aged under 2 has not been established.

Contraindications
Hypersensitivity to penicillins, and or cephalosporins and other beta-lactamase inhibitors.
Hypersensitivity to lidocaine (solvent for intramuscular use).
Children aged under 2.
Generally contraindicated during pregnancy and breastfeeding.

Precautions for use
During prolonged high dose therapy, periodic assessments of hematopoietic, kidney and liver function should be performed.
Yanoven contains 2.35 mEq (54 mg) of sodium per gram of piperacillin which may contribute in increasing the patient's total sodium intake. Since hypokalemia may occur in patients with low potassium reserves or in patients concomitantly taking potassium – reducing drugs, periodical testing for the electrolyte is recommended.
Serious and sometimes fatal hypersensitivity and anaphylactic reactions have been reported in patients treated with penicillin, including piperacillin/tazobactam compounds.
These reactions are more likely to occur in individuals with a history of hypersensitivity to multiple allergens, of asthma, hay fever and urticaria. Cross-allergy is possible with penicillin G., semi-synthetic penicillins and cephalosporins.
Careful history-taking regarding prior hypersensitivity to penicillins, cephalosporins and other allergens is therefore recommended before starting therapy with **Yanoven**.
If an allergic reaction occurs, the treatment should be discontinued and appropriate therapy instituted (with vasopressor amines, antihistamines, corticosteroids) or, in the case of anaphylaxis, immediate therapy with adrenaline (epinephrine) or other suitable emergency measures.
As with other penicillins, in the case of intravenous administration of higher than recommended doses, patients may experience neuromuscular excitability or convulsions.
Leukopenia and neutropenia may occur, especially after prolonged therapy.
Therefore, the hemopoietic should be checked frequently.
Use in patients with kidney impairment:
In patients with kidney impairment or undergoing dialysis, the intravenous dosage should be adjusted to the degree of kidney insufficiency.

Interactions
The contemporary administration of Probenecid with piperacillin / tazobactam causes a longer half-life and a lowering of renal clearance both of piperacillin and of tazobactam; however, the plasma concentrations of both drugs remain unaltered.
No interactions have been observed between piperacillin / tazobactam and Vancomycin or Tobramycin.
During the simultaneous administration of high doses of heparin, oral anti-coagulants and other drugs capable of affecting the blood coagulation system and/or the thrombocyte function, coagulation parameters should be tested more frequently and monitored regularly.
When used contemporarily with vecuronium, piperacillin may prolong the neuromuscular blocking action of vecuronium. Due to the similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-depolarizing muscle relaxants could be prolonged in the presence of piperacillin.
Piperacillin may reduce the clearance of methotrexate. Serum methotrexate levels should therefore be monitored frequently to prevent methotrexate-induced toxicity.
Interference with laboratory tests and other diagnostic tests
As per other penicillins, the administration of **Yanoven** may cause a false positive reaction regarding glucose in the urine; this happens when the the "reduction of copper test" is used. It is recommended the use of a test for the glucose, based on the enzymatic reaction.
There have been reports of positive test results using the Bio-Rad Laboratories Platelia Aspergillus EIA test in patients receiving piperacillin/tazobactam injection who were subsequently found to be free of Aspergillus infection. Non-Aspergillus polysaccharides and polyfuranose cross-reactions have been observed with the Platelia Aspergillus EIA test of the Bio-Rad Laboratories. Accordingly, positive results in patients treated with piperacillin/tazobactam need to be interpreted with care and confirmed by other diagnostic means.
The administration of piperacillin and tazobactam may result in a false positive reaction for the direct Coombs test.

Special warnings
As with other antibiotics, the prolonged use of penicillins may favor the development of penicillin – resistant microorganisms, including fungi, requiring the adoption of adequate therapy measures.
Bleeding manifestations have been occasionally reported in several patients treated with beta-lactam antibiotics. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time, and are most likely to occur in patients with renal insufficiency. If bleeding manifestations occur, **Yanoven** should be discontinued and appropriate therapy instituted.
Rare cases of pseudomembranous colitis have been observed correlatable to the use of antibiotic.
The symptoms of antibiotic – induced pseudomembranous colitis may be severe and persistent diarrhea that may become life-threatening.
The onset of pseudomembranous colitis symptoms may occur during or following antibacterial therapy.
It is important to consider this diagnosis in the case of significant diarrhea or colitis during therapy with **Yanoven**. Mild cases usually respond to drug discontinuation. In more severe cases; however, the use of fluids, electrolytes, protein supplements and, if required, treatment with oral vancomycin or oral teicoplanin are recommended. Peristalsis-inhibiting preparations are contraindicated.
Children aged under 2
Due to the lack of data concerning children aged under 2, the use of **Yanoven** for such patients is not recommended.

Pregnancy and lactation
There are no adequate and well-controlled studies with the piperacillin / tazobactam combination or with piperacillin or tazobactam alone in pregnant women. Piperacillin and Tazobactam cross the placenta.
This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the pregnant woman and to the fetus.
Piperacillin is excreted in low concentrations into human milk; tazobactam levels in human milk have not been studied. This drug should be used during nursing only if the potential benefit justifies the potential risk to the woman and to the infant.

Driving and using machines
The product does not interfere with driving and operating any machines.

Dosage and administration
Yanoven 2 g + 0.25 g can be administered by intramuscular route, slow intravenous injection (duration of at least 3-5 minutes) or by intravenous infusion (duration 20-30 minutes).
The lidocaine solvent ampoule, included in the packaging of **Yanoven** 2 g + 0.25 g, is used only for the intramuscular route.
Yanoven 4 g + 0.5 g can be administered only by slow intravenous injection or by intravenous infusion.
Dosage in patients over 12 years of age
The usual dosage for adults and for juveniles aged 12 and up with normal renal function is 2 g / 0.25 g of piperacillin / tazobactam every 12 hours by intramuscular injection; by intravenous administration dosage ranges from a minimum of 2 g / 0.25 g up to a maximum of 4 g / 0.5 g of piperacillin / tazobactam administered every 6, 8 or 12 hours. When **Yanoven** is used in the presumptive monotherapy of infections in adult patients with febrile neutropenia, the suggested dosage is 4 g / 0.5 g of **Yanoven** every 6-8 hours administered intravenously.
Children with intra-abdominal infections
In the case of children aged between 2 and 12, weighing up to 40 Kg and with normal kidney function, the suggested dosage per kilogram of body weight is 100 mg of piperacillin / 12.5 mg of tazobactam every 8 hours, administered by slow intravenous infusion. In the case of children aged between 2 and 12, weighing more than 40 Kg and with normal kidney function, the suggested daily dosage is 4 g of piperacillin / 0.5 g of tazobactam every 8 hours, administered by slow intravenous infusion.
Therapy duration should be adjusted according to infection severity and to the patient's clinical and bacteriological response. It is recommended that the therapy be protracted for at least 5 days, up to a maximum of 14 days, considering that administration should continue for another 48 hours after resolution of all clinical signs and symptoms.
Children aged under 2
Since no data are available for children aged under 2, Yanoven is not recommended for this age group.
Renal insufficiency in subjects aged over 12
In patients with renal insufficiency, the intravenous dose should be adjusted to the degree of insufficiency of renal function. Suggested daily doses are as follows:

Creatinine Clearance (ml/min)	Recommended Yanoven dosage
> 40	No dosage adjustment is necessary
20 - 40	Maximum dosage suggested: 4 g / 0.5 g every 8 hours
< 20	Maximum dosage suggested: 4 g / 0.5 g every 12 hours

For patients on hemodialysis, the maximum daily dosage is 8 g / 1 g of piperacillin / tazobactam. Because hemodialysis removes from 30% to 50% of piperacillin in 4 hours, patients on hemodialysis should receive a 2 g / 0.250 g vial following each dialysis period. For patients with renal impairment and renal insufficiency, measurement of serum levels of piperacillin and tazobactam will provide additional guidance for adjusting dosage.
Renal insufficiency in subjects aged between 2 and 12
Since the pharmacokinetics of piperacillin / tazobactam have not been studied in pediatric patients with renal insufficiency, changes of the dosage indicated in the following table should be considered as purely indicative.
Each patient should be closely monitored for the onset of any signs of drug toxicity. Drug dosage and intervals then should be consequently adjusted.
In general, the following dosage adjustments are recommended for pediatric patients with renal insufficiency aged between 2 and 12:

Creatinine Clearance (ml/min)	Recommended dosage of Yanoven
> 50 ml/min	(100 mg piperacillin / 12.5 mg tazobactam)/Kg every 8 hours, by slow intravenous infusion
≤ 50 ml/min	(70 mg piperacillin / 8.75 mg tazobactam)/Kg every 8 hours, by slow intravenous infusion

Patients with hepatic impairment
In patients with altered hepatic function no dosage adjustment is required.
Duration of Therapy
Therapy duration varies depending on the course of illness and clinical and bacteriological response of patients.
Therapy would last for a minimum of 5 days and a maximum of 14 days, and should be continued for another 48 hours after resolution of clinical symptoms or fever.

INSTRUCTIONS FOR RECONSTITUTION AND DILUTION
A. Intramuscular administration
Yanoven 2 g + 0.25 g must be reconstituted using lidocaine hydrochloride 0.5 % solvent included in the packaging.
The solvent with lidocaine is for intramuscular use only.
Do not exceed the dosage of 2 g + 0.25 g of piperacillin/tazobactam per injection site.
Do not administer Yanoven 4 g + 0.5 g by intramuscular injection.
Follow the instructions for reconstitution indicated below:
1) Shake the powder vial until the powder is detached from the bottom of the vial.
2) Remove the plastic cap to expose the central portion of rubber stopper and keep it (Pic. 1). Avoid touching the central portion of rubber cap.
3) Draw the lidocaine hydrochloride solvent into the syringe and inject it into the powder vial.
4) Cover the rubber stopper with the plastic cap to avoid touching with the fingers its central portion. Shake until the powder is completely dissolved. Shaking constantly, the reconstitution should take place within 10 minutes (Pic. 2).
5) Keep the solution aside until the foam disappears and a clear solution is obtained.
6) Remove the rubber cap and draw the solution into a 5 ml syringe for intramuscular administration.


Pic. 1


Pic. 2

B. Intravenous administration
To be administered only by healthcare professionals.
Intravenous administration
Reconstitute the product with the quantity of solvent indicated in the following table, using one of the compatible solutions listed below. Shake until completely dissolved. Shaking constantly, the reconstitutions should take place within 10 minutes.

Vial content (piperacillin / tazobactam)	Quantity of solvent to be added
Yanoven 2 g + 0.25 g	10 ml
Yanoven 4 g + 0.5 g	20 ml

Compatible solutions
- Water for injection
- Saline solution
- Saline solution with benzyl alcohol
- Saline solution with parabens
- Dextrose 5 %

Shake the powder vial until the powder is detached from the bottom of the vial.
Draw one of the solvents indicated above into the syringe and inject it into the powder vial.
Shake until the powder is completely dissolved.
Shaking constantly, the reconstitution should take place within 10 minutes.
Keep the solution aside until the foam disappears and a clear solution is obtained.
Before drawing the reconstituted solution into the syringe, ensure that the powder is completely dissolved.
If reconstitution has been carried out as described, the solution in the syringe shall contain the quantity of piperacillin and tazobactam declared on the label.
The reconstituted solution can be further diluted to the required volume (50-150 ml) using a compatible intravenous diluents solution listed below:
- Water for injection (The maximum recommended volume of water for injection is 50 ml per dose).
- Saline solution
- Glucose solution 5%
- Dextran 6% in saline solution

Incompatibility
Whenever **Yanoven** is to be administered together with other antibiotics (for example aminoglycosides), the drugs should be administered separately. The *in vitro* admixture of **Yanoven** with an aminoglycoside may cause substantial deactivation of the action of the aminoglycoside.
In the case of intramuscular administration, piperacillin / tazobactam and aminoglycosides should be reconstituted and administered separately in different injection sites.
Yanoven should not be mixed with other drugs in the same syringe or infusion bottle, since compatibility has not been established.
Yanoven should not be used with solutions containing sodium bicarbonate alone because of its chemical instability.
Yanoven should not be added to haematic products or to albumin hydrolysates.

Overdosage
There have been postmarketing reports of overdose with piperacillin / tazobactam. The majority of those events experienced, including nausea, vomiting and diarrhea, have also been reported with the usual recommended dosages. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).
Treatment should be supportive and symptomatic according to the patient's clinical conditions. Excessive serum concentrations of either piperacillin or tazobactam may be reduced by hemodialysis.

Adverse reactions

Adverse reactions are listed by target organs and systems and are subdivided by decreasing order of frequency as follows:
- Very common = reactions occurring with a ≥ 10% frequency
- Common = reactions occurring with a ≥ 1% frequency
- Uncommon = reactions occurring with a ≥ 0.1% to < 1% frequency
- Rare = reactions occurring with a ≥ 0.01% to < 0.1% frequency
- Very rare = reactions occurring with a < 0.01% frequency.

Infections and infestations: Uncommon: superinfection by Candida.
Blood and lymphatic system: Uncommon: leucopenia, neutropenia, thrombocytopenia. Rare: anemia, bleeding events (including purpura, epistaxis, prolongation of bleeding time), eosinophilia, hemolytic anemia. Very rare: agranulocytosis, positive direct Coombs test, protracted partial thromboplastin time, protracted prothrombin time, thrombocytosis.
Immune system disorders: Uncommon: Hypersensitivity reactions. Rare: anaphylactic / anaphylactoid (including shock) reactions.
Metabolic and nutritional disorders: Very rare: decrease in blood albumin, decreased glycemia, decreased total blood protein, hypokalemia.
Nervous system disorders: Uncommon: headache, insomnia.
Vascular disorders: Uncommon: hypotension, phlebitis, thrombophlebitis. Rare: flushing.
Gastro-intestinal disorder: Common: diarrhea, nausea, vomiting. Uncommon: constipation, dyspepsia, jaundice, stomatitis. Rare: stomach pain, pseudomembranous colitis.
Hepato-biliary disorders: Uncommon: increased alanine aminotransferase, increased aspartate aminotransferase. Rare: increased bilirubin, increased blood alkaline phosphate, increased gammaglutamyltransferase, hepatitis.
Cutaneous and subcutaneous disorders: Common: rash. Uncommon: itching, urticaria. Rare: pemphigus, multiform erythema. Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis.
Musculoskeletal, connective tissue and bone disorders: Rare: arthralgia.
Kidney and urinary disorders: Uncommon: increased blood creatinine. Rare: interstitial nephritis, kidney failure. Very rare: increased uremia.
General and injection site disorders: Uncommon: fever, reaction at injection site. Rare: rigidity.
Therapy with piperacillin has been associated with increased occurrence of fever and rash in patients suffering from cystic fibrosis.
Compliance with the instructions included in the leaflet reduces the risk of adverse reactions.
If you notice any adverse reactions listed or unlisted in this leaflet, please tell your doctor or pharmacist.

Shelf-life and storage conditions

See the expiry date printed on the outer carton.
This date refers to the product stored correctly in unopened package.
Beware not to use **Yanoven** after this date.
Store below 30°C.
After reconstitution using the appropriate solvent, the solutions for intravenous and intramuscular use are stable for 24 hours if stored at room temperature and for 48 hours if refrigerated (2 - 8°C). Unused solutions must be discarded.
Keep the medicine out of reach of children.

Composition

Yanoven 2 g + 0.25 g sterile powder and solvent for I.M. injectable solution
Each vial contains: Active ingredients: piperacillin sodium 2.085 g (equivalent to 2 g of piperacillin), tazobactam sodium 0.2683 g (equivalent to 0.25 g of tazobactam).
Each solvent ampoule contains: lidocaine hydrochloride 0.5%, water for injection.
Yanoven 4 g + 0.5 g sterile powder for solution for I.V. infusion
Each vial contains: Active ingredients: piperacillin sodium 4.170 g (equivalent to 4 g of piperacillin), tazobactam sodium 0.5366 g (equivalent to 0.5 g of tazobactam).

Pharmaceutical form and contents of the pack

- Sterile powder and solvent for I.M. injectable solution.

1 powder vial of 2 g + 0.25 g of piperacillin and tazobactam and 1 solvent ampoule of 20 mg/ 4 ml of lidocaine hydrochloride.
The solvent with lidocaine is for intramuscular use only.
- Sterile powder for solution for I.V. infusion.

1 powder vial of 4 g + 0.5 g of piperacillin and tazobactam.

Manufactured by: **Mitim S.R.L.**
Brescia, Italy
For: **ARWAN Pharmaceutical Industries Lebanon s.a.l.**
Jadra, Lebanon

THIS IS A MEDICAMENT

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists