TAGIX®
(Tigecycline)

INDICATIONS
Tagix is indicated in infections caused by susceptible strains of the designated microorganisms in the conditions listed below for patients 18 years of age and older:
Complicated skin and skin structure infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible and resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus grp.* including *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes and Bacteroides fragilis*.
Complicated intra-abdominal infections caused by Citrobacter freundii, Enterobacter cloacae, Escherichia *coli*, *Klebsiella oxytoca*, *Klebsiella pneumonia*, *enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin susceptible isolates only), *Streptococcus anginosus grp.* including *S. anginosus*, *S. intermedius*, and *S. constellatus*, Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteriden vulgates, clostridium perfringens, and peptococcus micros.
Appropriate specimens for bacteriological examination should be obtained In order to isolate and identify the causative organisms and to determine their susceptibility tigecycline. Tagix may be initiated as empiric monotherapy before results of these tests are known.
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Tagix and other antibacterial drugs, Tagix should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

DOSAGE AND ADMINISTRATION
The recommended dosage regimen for Tagix is an initial dose of 100 mg, followed by 50 mg every 12 hours.
Intravenous (IV) Infusions of Tagix should be administered over approximately 30 to 60 minutes every 12 hours.
The recommended duration of treatment with Tagix for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 to 14 days. The duration of therapy should be guided by the severity and site of the infection and the patient's clinical and bacteriological progress. No dosage adjustment is warranted in patients with mild to moderate hepatic impairment.
In patients with severe hepatic impairment, the initial dose of Tagix should be 100 mg followed by a reduced maintenance dose at 25 mg every 12 hours, Patients with severe hepatic impairment should be treated with caution and monitored for treatment response.
No dosage adjustment of Tagix is necessary in patients with renal impairment or in patients undergoing hemodialysis.
No dosage adjustment of Tagix is necessary based on age, gender, or race.

Preparation and Handling
Each vial of Tagix should be reconstituted with 5.3 ml of 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, to achieve a concentration of 10 mg/ml of tigecycline. (Note: Each vial contains a 6% overage. Thus, 5 ml of reconstituted solution is equivalent to 50 mg of the drug) The vial should be gently swirled until the drug dissolves.
Withdraw 5 ml of the reconstituted solution from the Vial and add to a 100 ml IV bag for infusion for a 100 mg dose, reconstitute two vials; for a 50 mg dose, reconstitute one vial). The maximum concentration in the IV bag should be 1 mg/ml. The reconstituted solution should be yellow to orange in color; If not, the solution should be discarded.
Parenteral drug products should be inspected visually for particulate matter and discoloration (e.g. green or black) prior to administration. Once reconstituted, Tagix may be stored at room temperature for up to 24 hours (up to 6 hours in the vial and the remaining time in the IV bag). Alternatively, Tagix may be stored ref refrigerated at 2° to 8°C (36° to 46°F) for up to 45 hours following Immediate transfer of the reconstituted solution into the IV bag.
Tagix may be administered intravenously through a dedicated line or though a Y-site. If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of Tagix with either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection. USP,. Injection should be made with an infusion solution compatible with tigecycline and with any other drug(s) administered via this common line.

Compatibilities/Incompatibilities
Compatible intravenous solutions include 0.9% sodium chloride injection. USP, and 5% dextrose injection, USP. When administered through a Y-site, Tagix is compatible with the following drugs or diluents: amikacin, dobutamine, dopamine HCl, gentamicin, haloperidol lactated Ringer's, lidocaine HCl, morphine, norepinephrine, piperacillin/tazobactam (EDTA formulation), potassium chloride, propofol, ranitidine HCl, theophylline, and tobramycin.
The following drugs should not be administered simultaneously through the same Y-site as Tagix: Amphotericin B and diazepam.

CONTRAINDICATIONS
Tigecycline is contraindicated for use in patients who have known hypersensitivity to tigecycline.

WARNINGS
Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including tigecycline, and may be life-threatening.
Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics and may have similar adverse effects. Tigecycline should be administered with caution in patients with known hypersensitivity to tetracycline class antibiotics.
Tigecycline may cause fatal harm when administered to a pregnant woman. If the patient becomes pregnant while taking tigecycline, tile patient should be apprised to the potential hazard to the fetus. Results of animal studies indicate that tigecycline crosses the placenta and is found in fetal tissues. Decreased fetal weights in rats and rabbits (With associated delays in ossification) and fetal loss in rabbits have been observed with tigecycline.
The use of Tigecycline during tooth development (last half of pregnancy, infancy, and childhood to the 8 years) may cause permanent discoloration of the teeth (yellow-gmy-brown). Results of studies in rats with Tigecycline have shown bone discoloration, Tigecycline should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Tigecycline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS
General
Abnormalities In total bilirubin concentration, prothrombin time and transaminases have been seen in patients treated with tigecycline. Isolated cases of significant hepatic dysfunction and hepatic failure have been reported In patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications.
Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing tigecycline therapy. Adverse events may occur after the drug has been discontinued.
Caution should be exercised when, considering Tigecycline monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. In phase 3 cIAI studies more patients treated with tigecycline versus imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock but due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established.
Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics and may have similar adverse effects. Such effects may include,: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia. acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of tigecycline.
The safety and efficacy of tigecycline in patients with hospital acquired pneumonia have not been established.
As with other antibacterial drugs, use of tigecycline may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.
Prescribing tigecycline in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and Increases the risk of the development of drug-resistant bacteria.

Information for Patients
Patients should be counseled that antibacterial drugs including Tigecycline should only be used to treat bacterial infections. They do not treat viral Infections (e.g. the common cold). When Tigecycline is prescribed to treat a bacterial infection patients should be told that although It IS common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Tigecycline or other antibacterial drugs in the future.
Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Lifetime studies in animals have not been performed to evaluate the carcinogenic potential of tigecycline. No mutagenic or clastogenic potential was found in a battery of tests, including in vitro chromosome aberration assay in Chinese hamster ovary (CHO) cells, *in Vitro* forward mutation assay in CHO cells (HGRPT locus), in vitro forward mutation assays in mouse lymphoma cells, and *in vivo* mouse micronucleus assay. Tigecycline did not affect mating or fertility in rats at exposures up to 5 times the human daily dose based on AUC. In female rats, there were no compound-related effects on ovaries or estrous cycles at exposures up to 5 times tile human daily dose based on AUC.

Pregnancy
Teratogenic effects Category D
Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, ^{14}C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures. The administration of tigecycline was with slight reductions in fetal weights and an increased incidence of minor skeletal anomalies (delays in bone Ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively. An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.
There are no adequate and well-controlled studies of tigecycline, in pregnant women. Tigecycline should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Results from animal studies using ^{14}C-labeled tigecycline is excreted indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.
It Is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Tigecycline is administered to a nursing woman.

Use in Patients with Hepatic Impairment
No dosage adjustment is warranted in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment should be treated with caution and monitored for treatment response.

Pediatric use
Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Therefore, use in patients under 18 years of age is not recommended

Geriatric use
No unexpected overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.

Drug Interactions
Tigecycline (100 mg followed by 50 mg every 12 hours) and digoxin (0.5 mg followed by 0.25 mg orally every 24 hours) were coadministered to healthy subjects in a drug Interaction study. Tigecycline slightly decreased the C^{max} of digoxin by 13%, but did not affect the AUC or clearance of digoxin. This small change In C^{max}, did not affect the steady-state pharmacodynamic effects of digoxin as measured by changes In ECG intervals. In addition, digoxin did not affect the pharmacokinetic profile of tigecycline. Therefore, no dosage adjustment of either drug is necessary when Tigecycline Is administered with digoxin.
Concomitant administration of Tigecycline (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg Single-dose) to healthy subjects resulted in a decrease in clearance of R-warfarin and S-warfarin by 40% and 23%, an increase in C^{max} by 38% and 43% and an increase in AUC by 68% and 29%, respectively. Tigecycline did not significantly alter the effects of warfarin on INR. In addition, warfarin did not affect the pharmacokinetic profile of tigecycline. However, prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin.
In vitro studies in human liver microsomes Indicate that tigecycline does not inhibit metabolism mediated by any of the following 6 cytochrome P450 (CYP) isoforms: IA2, 2CB, 2C9, 2C19, 2D6, and 3A4. Therefore, Tigecycline is not expected to alter the metabolism of drugs metabolized by these enzymes. In addition, because tigecycline is not extensively metabolized, clearance of tigecycline is not expected to be affected by drugs that inhibit or induce the activity of these CYP450 isoforms.
Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin.
Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.

Drug/laboratory Test Interactions
There are no reported drug-laboratory test interactions.

SIDE EFFECTS
The table below shows the Incidence of treatment-emergent Adverse events through test of cure reported in ≥2% of patients in phase 3 studies regardless of causality.

Body System Adverse Events	Tigecycline[a] (n= 1415)	Comparator[b] (n= 1382)
Body as a whole		
Abdominal pain	6.8	5.7
Abscess	3.2	2.6
Asthenia	2.5	1.7
Back pain	1.2	2.3
Fever	7.1	9.8
Headache	5.9	6.5
Infection	8.3	5.4
Pain	3.7	2.9
Cardiovascular System		
Hypertension	4.9	5.6
Hypotension	2.3	1.7
Phlebitis	1.8	3.8
Digestive system		
Constipation	2.8	4.1
Diarrhea	12.7	10.8
Dyspepsia	2.9	1.6
Nausea	29.5	15.8
Vomiting	19.7	10.8
Hemic and lymphatic system		
Anemia	4.2	4.8
Leukocytosis	3.7	2.5
Thrombocythoemia	6.1	6.2
Metabolic and Nutritional		
Alkaline Phosphatase increased	3.5	2.6
Amylase Increased	3.1	1.4
Bilubinemia	2.3	0.9
BUN increased	2.1	0.2
Healing abnormal	3.5	2.6
Hyperglycemia	1.8	2.9
Hypocalemia	2.1	2.9
Hypoproteinemia	4.5	3
Lactic dehydrogenase increased	4	3.5
Peripheral edema	3.3	3.3
SGOT increased	4.3	4.4
SGPT increased	5.6	4.7
Nervous System		
Dizziness	3.5	2.7
Insomnia	2.3	3.3
Respiratory system		
Cough increased	3.7	3.8
Dyspnea	2.9	2.7
Pulmonary physical finding	1.9	2.2
Skin and appendages		
Pruritis	2.6	4.1
Rash	2.4	4.1
Sweating	2.3	1.6
Others		
Local reaction to procedure	9	9.1

[a] 100 mg initially. followed by 50 mg every 12 hours
[b] Vancomycin/Aztreonam, Imipenem/Cilastatin, Linezolid
[c] LFT abnormalities in Tigecycline treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occured more often in therapy.

The following drug-related adverse events were reported infrequently (≥0.2% and <2%) in patients receiving Tigecycline in Phase 3 clinical studies:
Body as a Whole: injection site inflammation. injection site pain, injection site reaction, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis
Cardiovascular System: thrombophlebitis, bradycardia, tachycardia, vasodilatation
Digestive System: anorexia, dry mouth, jaundice, abnormal stools
Metabolic/Nutritional System: Increased creatinine, hypocalcemia, hypoglycemia, hyponatremia
Nervous System: somnolence
Special Senses: taste perversion
Hemic and Lymphatic System: prolonged activated partial thromboplastin time (aPTT), prolonged prothrombin time (PT), eosinophilia. increased international normalized ratio (INR), thrombocytopenia
Urogenital system: vaginal moniliasis, vaginitis, leukorrhea

OVERDOSAGE
No specific information is available on the treatment of overdosage with tigecycline. Intravenous administration of Tigecycline at a Single dose of 300 mg over 60 minutes in healthy volunteers resulted In an increased incidence of nausea and vomiting. In single-dose IV toxicity studies conducted with tigecycline In mice, the estimated median lethal dose (LD_{50}) was 124 mg/kg in males and, 98 mg/kg in females. In rats, the estimated LD_{50} was 106 mg/kg for both sexes.
Tigecycline is not removed In significant quantities by hemodialysis.

STORAGE
Store below 30°C.

PRESENTATION
Vials:
TAGIX 50 mg: Tigecycline 50 mg/vial
Excipients: Lactose, Water for injection, HCl and/or NaOH for pH adjustment.

Council of Arab Health Ministers, Union of Arab Pharmacists

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its 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.

HIKMA Pharmaceuticals,
Amman-Jordan

Keep medicament out of the reach of children.

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