SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TİGENEX 50 mg Powder for Solution for Infusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient:
Tigecycline
Each 5 ml vial of TİGENEX contains 50 mg of lyophilized tigecycline powder for intravenous infusion.
When prepared for use, the solution contains 10mg/ml tigecycline.

Excipients:
For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Concentrated powder for solution for intravenous infusion, sterile.
Orange colored lyophilized powder.
The solution for infusion is an orange or dark orange solution without visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

TİGENEX should only be used when other alternatives are known or suspected to be unsuitable.

TİGENEX is indicated for the treatment of the following infections in adults:
-Complicated skin and skin structure infections, including methicillin-resistant *Staphylococcus aureus* (MRSA)
- Complicated intra-abdominal infections
- Community-acquired bacterial pneumonia caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), *Haemophilus influenza* (beta-lactamase-negative isolates), and *Legionella pneumophila*, including cases with bacteremia.

TİGENEX is not indicated for the treatment of diabetic foot infection. *(see, Section 5.2.).*
The clinical trial to demonstrate that TİGENEX is non-inferior in the treatment of diabetic foot infection was unsuccessful.

4.2. Posology and method of administration

Posology/frequency and duration of administration:
It is administered by the intravenous route; it is used as 50 mg every 12 hours after an initial dose of 100 mg. The recommended duration of treatment in the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections is 5-14 days. The

recommended duration of treatment for community-acquired bacterial pneumonia is 7-14 days. The duration of treatment should be determined according to the severity of the infection and the body region where it is located, as well as the clinical and bacteriological course of the patient.

Route of administration:
TİGENEX is administered by intravenous infusion. The infusion time should be approximately 30-60 minutes.

Additional information on special populations:
Renal Impairment:
No dose adjustment is required in patients with renal impairment or on hemodialysis. *(see, Section 5.2).*

Hepatic impairment:
No dose adjustment is required in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the dose of TİGENEX should be reduced to 25 mg every 12 hours after an initial dose of 100 mg. Patients with severe hepatic impairment should be treated with caution and the response to therapy monitored (see sections 4.4 and 5.2).

Pediatric population:
TİGENEX should not be used in children younger than 8 years old due to color changes that may occur in the teeth. In children younger than 18 years of age, TİGENEX is not recommended for use in this age group, as its safety and efficacy have not been established.

Geriatric population:
No dosage adjustment is required in elderly patients. *(see, Section 5.2).*

4.3. Contraindications
TİGENEX is contraindicated in patients with known hypersensitivity to tigecycline or any ingredient in the drug.

Patients hypersensitive to tetracycline class antibiotics may also be hypersensitive to tigecycline.

4.4. Special warnings and precautions for use

In phase 3 and 4 clinical studies, an increase in all-cause mortality was observed in patients treated with TİGENEX relative to the comparison agent. The reason for the 0.6% (95% CI, 0.1, 1.2) mortality risk difference could not be determined. TİGENEX should only be used when other alternatives are known or suspected to be unsuitable.

In the batch analysis of 13 Phase 3 and Phase 4 clinical studies containing the comparator, death occurred in 4.0% (150/3788) of patients receiving tigecycline and 3.0% (110/3646) of patients receiving comparator; this made the unadjusted risk difference 0.9% (95% CI, 0.1, 1.8). In the batch analysis of these studies, the difference in adjusted all-cause mortality risk between patients treated with tigecycline and the comparator was 0.6% (95% CI, 0.1, 1.2) based on the study weight random effect model. Mortality analysis in all studies (including post-marketing studies) for the approved indications showed an adjusted mortality rate of 2.5% (66/2640) and 1.8% (48/2628) between tigecycline and comparison agent, respectively. The adjusted risk difference for mortality adjusted for study weight was 0.6% (95% CI, 0.0, 1.2).

The reason for this increase has not been determined. Death is usually the result of worsening infection, complications of infection, or underlying comorbidity. TİGENEX should only be used when other alternatives are known or suspected to be unsuitable.

Anaphylactic/anaphylactoid reactions have been reported with treatment with almost all antibacterial agents, including tigecycline, and may be life-threatening.
Severe cases of pseudomembranous colitis, ranging from mild to life-threatening, have been reported with almost all antibacterial agents. Therefore, it is important to consider this picture in patients presenting with diarrhea after any antibiotic treatment.

Non-healing of surgical wounds has been associated with superinfection in clinical studies in patients with complicated intra-abdominal infections. Patients with a non-healing wound condition should be monitored for the detection of superinfection. Patients who develop superinfection, particularly nosocomial pneumonia, appear to be associated with poor outcomes. Patients should be followed closely against the risk of developing superinfection. If a focus of infection other than complicated skin and skin structure infections or complicated intra-abdominal infections is determined after the initiation of TİGENEX treatment, initiation of an alternative antibacterial therapy that has been shown to be effective in the treatment of the specific type of infection should be considered.

Cases of cholestatic liver injury, including fatal cases of hepatic failure, have been reported in patients receiving tigecycline therapy. Hepatic failure may occur in patients treated with tigecycline due to the underlying condition or multiple drug use.

The effect of cholestasis on tigecycline pharmacokinetics has not been fully established. Approximately 50% of the total tigecycline excretion is excreted in the bile. Therefore, patients with cholestasis should be closely monitored.

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. Tigecycline may show a side effect profile similar to tetracycline group antibiotics. These side effects may be photosensitivity, pseudotumor cerebri, pancreatitis, and anti-anabolic effects (elevated BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TİGENEX. Therefore, its use should be avoided in patients with hypersensitivity to tetracycline class antibiotics.

Acute pancreatitis (frequency: uncommon) that can be serious has been seen in association

with tigecycline therapy (*see section 4.8*). A diagnosis of acute pancreatitis should be considered when clinical signs, findings, or laboratory abnormalities suggestive of acute pancreatitis develop in patients receiving tigecycline. Most reported cases developed after at least one week of treatment. Cases of patients without known risk factors for pancreatitis have been reported. Patients usually improve after tigecycline treatment is discontinued. In patients with suspected pancreatitis, discontinuation of tigecycline therapy should be considered.

There is limited experience with the use of tigecycline in the treatment of infections in people with a serious underlying disease.

In clinical trials in complicated skin and subcutaneous tissue infections, the most common infections in patients treated with tigecycline were cellulitis (58.6%), followed by major abscess (24.9%). Patients with serious underlying disease, such as an immunosuppressive decubitus ulcer infection, or an infection requiring treatment for more than 14 days (for example, necrotizing fasciitis) were excluded from clinical trials. Few patients with comorbid factors such as diabetes (25.8%), peripheral vascular disease (10.4%), intravenous drug addiction (4%), and HIV-positive infection (1.2%) were included. There is also limited experience in the treatment of patients with concomitant bacteremia (3.4%). Therefore, caution is advised when treating such patients. In the results of a study conducted in a group of patients with diabetic foot infection, tigecycline showed less efficacy than the compared drug. Therefore, the use of tigecycline in these patients is not recommended.

In clinical trials in complicated intra-abdominal infections, the most common infections in patients treated with tigecycline were complicated appendicitis (50.3%), followed by less-reported complicated cholecystitis (9.6%), bowel perforation (9.6%), intra-abdominal abscess (8.7%), and gastric and intra-abdominal infections. duodenal ulcer (8.3%), peritonitis (6.2%), complicated diverticulitis (6.0%). Surgically occurring peritonitis is present in 77.8% of these patients. There is a limited number of immunocompromised patients with a serious underlying disease (APACHE II score > 15 (3.3%)) or multiple intra-abdominal abscesses (11.4%) that occur surgically. There is limited experience in the treatment of patients with concomitant bacteremia (5.6%). Therefore, caution should be exercised during the treatment of these patients. Bone discoloration was observed in the results of tigecycline studies in rats. TİGENEX may be associated with permanent discoloration of teeth when administered during tooth development in humans.

It should be avoided when considering tigecycline monotherapy in patients with complicated intra-abdominal infections after clinically significant bowel perforation. In the phase III complicated intra-abdominal infection studies (n=1642), 6 patients with bowel perforation and sepsis/septic shock were treated with tigecycline and 2 patients with imipenem/cilastatin. The APACHE II scores (mean = 13) of the 6 patients who received tigecycline were higher than the other 2 patients who received imipenem/cilastatin (APACHE II value = 4 and 6). Due to the difference in baseline APACHE II scores between the two treatment groups and the small number of patients, this result cannot be proven to be related to treatment.
Increases in total bilirubin concentration, prothrombin time and transaminase have been seen in patients treated with tigecycline. Isolated cases of significant hepatic impairment and dysfunction have been reported in patients receiving tigecycline therapy. Some of these patients have more than one concomitant drug use. Patients who develop abnormal liver

function tests during tigecycline therapy should be monitored for possible worsening of liver function and the risks and benefits of continuing tigecycline therapy should be evaluated. Liver failure may occur after discontinuation of the drug.

A study of patients with hospital-acquired pneumonia (including ventilator-associated pneumonia) failed in terms of efficacy and safety of TİGENEX. In this study, patients were randomized to receive tigecycline (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, patients were allowed to receive designated additional treatments. In the subgroup of ventilator-associated pneumonia patients given tigecycline, lower cure rates (70.1% vs 47.9% for the clinically evaluable population) and higher mortality (15/122 [12.3%] vs. comparator drug) 25/131 [19.1%]) were observed.

Among patients with ventilator-associated pneumonia and bacteremia developing in this background, higher mortality was observed in patients treated with tigecycline compared to patients treated with a comparator (9/18 [50.0%] vs. 1/13 [7.7%]).

Clostridium difficile-associated diarrhea has been reported with the use of nearly all antibacterial agents, including TİGENEX, and can range from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, resulting in the proliferation of *C. difficile*.

C. difficile produces toxins A and B, which cause pseudomembranous colitis. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections may be refractory to antimicrobial therapy and colectomy may be required. Pseudomembranous colitis should be considered in all diarrheal patients taking antibiotics. Medical history should be considered, as this has been reported to occur 2 months after the administration of antibacterial agents.

Antibiotics ineffective against *C. difficile* may need to be discontinued if pseudomembranous colitis is suspected or detected. Appropriate fluid and electrolyte management, protein supplementation, antibiotic therapy for C. difficile, and surgical evaluation should be initiated.

In severe patients with clinically significant bowel perforation or complicated intra-abdominal infections secondary to inevitable sepsis or septic shock, the need for combined antibacterial therapy should be considered when tigecycline therapy is administered.

If tigecycline is co-administered with anticoagulants, patients should be monitored with prothrombin time or other appropriate anticoagulation tests.

4.5. Interaction with other medicinal products and other forms of interaction

Studies have been done in adults only.

In a drug interaction study, TİGENEX (100 mg followed by 50 mg every 12 hours) and digoxin (0.25 mg followed by 0.25 mg every 24 hours) were administered to healthy volunteers. Tigecycline caused a slight (13%) decrease in $_{Cmax}$ of digoxin, but did not affect AUC (area under the curve) or clearance. This slight change in C_{max} did not alter the steady-

state pharmacodynamics of digoxin, as evidenced by changes in ECG interval measurements. The recommended dose of tigecycline does not affect the clearance of digoxin (0.25 mg followed by 0.25 mg daily) or the rate/scope of absorption when administered to adult healthy volunteers. Also, digoxin had no effect on the pharmacokinetic profile of tigecycline. Therefore, no dose adjustment is required when TİGENEX is used together with digoxin.

Co-administration of TİGENEX (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg single dose) to healthy volunteers resulted in a 40% and 23% reduction in R-warfarin and S-warfarin clearances, respectively, and 38% and 38% in C_{max}, respectively. There was an increase of 43% and an increase of 68% and 29% in AUC, respectively. This interaction mechanism has not yet been elucidated.

Tigecycline did not significantly alter the effects of warfarin on INR (International normalized ratio, PT). In addition, warfarin did not alter the pharmacokinetic profile of tigecycline.
Where tigecycline is co-administered with warfarin, monitoring with prothrombin time or another appropriate anticoagulation test is appropriate. Warfarin did not affect the pharmacokinetic profile of tigecycline.

In vitro studies with human liver microsomes have shown that metabolisms mediated by cytochrome P450 (CYP) isoforms 1A2, 2C8, 2C9, 2C19, 2D6 and 3A4 are not inhibited by tigecycline. Therefore, TİGENEX is not expected to alter the metabolism of other drugs metabolized by these enzymes.

Also, as tigecycline is not extensively metabolized, drugs that inhibit or stimulate these isoforms are not expected to affect the clearance of tigecycline. In vitro, tigecycline is neither a competitive nor an irreversible inhibitor of the CYP450 enzyme.

No antagonism was observed between tigecycline and other commonly used antibiotic classes in in vitro studies.

Concomitant use of antibiotics with oral contraceptives may reduce the effectiveness of oral contraceptives.
According to an in vitro study, tigecycline is a substrate of P-gp. Concomitant use with P-gp inhibitors (eg ketoconazole or cyclosporine) or P-gp inducers (eg rifampicin) may affect the pharmacokinetics of tigecycline.

Additional information on special populations:
No interaction studies have been conducted in special populations.

Pediatric population:
No interaction studies have been performed in the pediatric population.

4.6. Pregnancy and lactation
General advise
Pregnancy category: D

Women of childbearing potential / Contraception
Women of childbearing potential should use an appropriate and effective method of contraception.

Concomitant use of antibiotics with oral contraceptives may reduce the effectiveness of oral contraceptives.

Pregnancy
There are no or limited data on the use of tigecycline in pregnant women. Results of animal experiments have shown that TİGENEX causes reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
Due to the enrichment in the tissues with high calcium turnover and the formation of calcium chelate complexes, as it is known in tetracycline class antibiotics, when tigecycline is used in the second half of pregnancy and in children younger than 8 years old, it may cause permanent tooth damage (discoloration and enamel disorder) and delay in the ossification process in the fetus. TİGENEX should not be used during pregnancy unless the clinical situation requires treatment with tigecycline.
Tigecycline has not been studied for use before and during childbirth. TİGENEX should not be used during pregnancy unless necessary.

Lactation
It is not known whether this drug is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of tigecycline/metabolites in milk. (see Section 5.3). This risk cannot be excluded for newborns/infants. A decision should be made to discontinue/discontinue breastfeeding or tigecycline treatment, taking into account the benefit of breastfeeding the child and the benefit of the treatment for the woman.

Fertility
No effects on mating and fertility were observed in rats with administration of tigecycline at doses 4.7 times the human daily dose based on AUC (area under the curve). No active substance-related effects were observed in the ovarian or estrus cycle following administration of the same doses of tigecycline in female rats. There is insufficient information on fertility in humans.

4.7 Effects on ability to drive and use machines
TİGENEX may cause dizziness and therefore impair the ability to drive or operate machinery.

4.8 Undesirable effects
The total number of patients with complicated skin and skin structure infections and complicated intra-abdominal infections treated with tigecycline in phase III and IV clinical studies was 2393.

The most frequently reported drug-related adverse events requiring emergency treatment in clinical trials were reversible nausea (21%) and vomiting (13%). Usually, these side effects occur in the early period (1-2 days of treatment) and are usually mild or moderate.

Side effects reported with TİGENEX include clinical studies and post-marketing experience and are listed below.

Undesirable effects are listed according to the following categories: Very common (≥1/10); common (≥1/100 to < 1 /10); uncommon (≥1/1000 to <1/100); rare (≥1/10.000 to <1/1000); very rare (< 1/10.000); unknown (cannot be estimated from the available data).

Post-marketing experience with tigecycline has been derived from spontaneous reports and their frequency cannot be estimated. Therefore, they are classified as unknown.

Infections and infestations:
Common: Pneumonia, abscess, infections, sepsis/septic shock

Blood and lymphatic system diseases:
Common: Activated partial thromboplastin time prolongation (aPTT), prothrombin time prolongation (PT)
Uncommon: Thrombocytopenia, increased international normalized ratio (INR)
Unknown: Hypofibrinogenemia

Immune system diseases:
Unknown: Anaphylactic/anaphylactoid reactions* *(see sections 4.3 and 4.4)*

Metabolism and nutrition disorders:
Common: Bilirubinemia, hypoglycemia, hypoproteinemia

Nervous system diseases:
Common: Dizziness

Vascular diseases:
Common: Phlebitis
Uncommon: Thrombophlebitis

Gastrointestinal diseases:
Very Common: Nausea, vomiting, diarrhea
Common: Abdominal pain, anorexia, dyspepsia
Uncommon: Acute pancreatitis

Hepato-biliary diseases:
Common: Elevated serum aspartate aminotransferase (AST), elevated serum alanine aminotransferase (ALT), hyperbilirubinemia.
Uncommon: Jaundice, liver damage (mostly cholestatic)
Unknown: Hepatic impairment* *(see 4.4 Special warnings and precautions for use)*

Skin and subcutaneous tissue diseases:
Common: Itching, rash
Unknown: Serious skin reactions including Steven-Johnson syndrome*

General disorders and administration site conditions:
Common: Headache, abnormal tissue healing, injection site reactions
Uncommon: Inflammation, pain, edema and phlebitis at the injection site.

Researches:
Common: Elevated serum amylase, increased blood urea nitrogen (BUN).
* Post-marketing adverse reactions

Antibiotic class effects:
Pseudomembranous colitis of varying degrees from mild to life-threatening. *(see., section 4.4)*
Growth in non-susceptible organisms, including fungi (see section 4.4).

Tetracycline class effects:
Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics. Adverse reactions specific to the tetracycline class include photosensitivity, pseudotumor cerebri, pancreatitis, and anti-anabolic effect (elevated blood urea nitrogen (BUN), azotemia, acidosis, hyperphosphatemia) (see section 4.4).

Tigecycline may cause permanent discoloration of teeth when used during tooth development (see Section 4.4).

In clinical studies of phase 3 and 4 complicated skin and skin structure infections and complicated intra-abdominal infections, serious infection-related adverse events were reported more frequently in patients treated with tigecycline than with the comparator (7.1% vs. 5.3%). In terms of sepsis/septic shock, a significant difference was observed when the comparator (1.1%) was compared with tigecycline (2.2%).

Abnormalities of AST and ALT were more common in patients treated with tigecycline after treatment and during treatment in patients using the comparator.
In a batch analysis of 13 phase 3 and phase 4 studies using comparator, death was reported in 2.4% (54/2216) of patients receiving tigecycline and 1.7% (37/2206) of patients receiving comparator drugs.

In the batch analysis of these studies, the difference in risk of all causes of death between patients receiving comparator drugs and patients receiving tigecycline was 0.9% (95% CI 0.1, 1.8).

In the batch analysis of these studies, the difference in adjusted all-cause mortality risk between patients treated with tigecycline and the comparator was 0.6% (95% CI, 0.1, 1.2) based on the study weight random effect model.

No significant difference was observed between tigecycline and the comparator according to the type of infection. The reason for not obtaining balanced results on the subject could not be defined. In general, deaths have occurred as a result of underlying comorbidity or worsening or complications of infection.

The most frequently reported adverse reactions requiring immediate treatment during

TİGENEX treatment were nausea 26% (17% mild, 8% moderate, 1% severe) and vomiting 18% (11% mild, 6% moderate). severity, 1% severe). Nausea and vomiting usually occurred at the beginning of treatment (days 1-2).

Additional information on special populations:
Pediatric population:
Very limited safety data are available in the multiple dose pharmacokinetic (PK) study. No new or unexpected safety profile was observed with tigecycline in this study.

Reporting of suspected adverse reactions
If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose and treatment
There is no specific information about the treatment to be applied in case of overdose. Administration of TİGENEX as a single dose of 300 mg (intravenous over 60 minutes) to healthy volunteers resulted in increased nausea and vomiting. Significant excretion of tigecycline by hemodialysis is not possible.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties
Pharmacotherapeutic Group: Systemically used antibacterial drugs, Tetracyclines
ATC Code: J01AA12

Mechanism of Action:
Tigecycline binds to the 30S subunit of ribosomes in bacteria, blocking the entry of amino-acyl tRNA molecules into the A region of the ribosome, and inhibits protein translation. This prevents the entry of amino acid molecules into the elongated peptide chain. In addition, tigecycline has the ability to oppose two important tetracycline resistance mechanisms, ribosomal protection and efflux. Therefore, tigecycline has been shown to have in vitro and in vivo activity against a broad spectrum of bacterial pathogens. Eflux pump-induced multidrug resistance (MDR) has been demonstrated between tigecycline and minocycline-resistant strains in *Enterobacteriaceae*.

No target cross-resistance has been observed between tigecycline and many other antibiotics. *In vitro* studies did not reveal any antagonistic effects between tigecycline and other commonly used antibiotics.

Tigecycline is sensitive to the chromosomally encoded multidrug efflux pump of Proteeae and Pseudomonas aeruginosa. Proteeae family pathogens (*Proteus spp., Providencia spp. and Morganella spp.*) It is generally less sensitive to tigecycline than other strains of the Enterobacteriaceae. The decreased sensitivity in both groups was attributed to overexpression of the nonspecific AcrAB multi-drug efflux pump. Reduced susceptibility in *Acinetobacter baumannii* is attributed to overexpression of the AdeABC efflux pump.

Tigecycline is generally considered to be bacteriostatic. With tigecycline at a concentration of 4 times the minimum inhibitory concentration (MIC), a 2-log decrease is observed in colony counts against *Enterococcus* strains, *Staphylococcus aureus* and *Escherichia coli*. A partial bactericidal effect and a 3-log reduction were observed with tigecycline against *Neisseria gonorrhea*.
Tigecycline has also shown bactericidal activity against common respiratory strains such as *S. pneumoniae, H. influenzae* and *L. pneumophila*.
Where possible, the clinical microbiology laboratory should provide physicians with periodic reports describing the cumulative *in vitro* susceptibility test results of antimicrobial drugs used in local hospitals and practice areas, and the susceptibility profile of nosocomial and community-acquired pathogens. These reports will assist physicians in selecting the most effective antimicrobial drug.

The minimum inhibitory concentration (MIC) threshold values published by the European Committee Antimicrobial Susceptibility Test (EUCAST) are as follows.

Staphylococcus spp. $S \leq 0.5$ mg/L and $R > 0.5$ mg/L

Except *S. pneumoniae, Streptococcus spp.* $S \leq 0.25$ mg/L and $R > 0.5$ mg/L

Enterococcus spp. $S \leq 0.25$ mg/L and $R > 0.5$ mg/L

Enterobacteriaceae $S \leq 1$(^) mg/L and $R > 2$ mg/L

(^) Tigecycline has decreased in vitro activity against *Proteus, Providencia* and *Morganella spp.*

Although there is clinical evidence of efficacy for anaerobic bacteria in polymicrobial intra-abdominal infections, there is no correlation between MIC values, pharmacokinetic / pharmacodynamic PK/PD data and clinical outcomes. Therefore, a threshold value of sensitivity was not given. It should be noted that the MIC distribution for *Bacteroides* and *Clostridium* organisms is wide and may contain values exceeding 2 mg/L tigecycline.

There is limited evidence of clinical efficacy of tigecycline against *enterococci*. In addition, it has been shown in clinical studies that polymicrobial intra-abdominal infections respond to tigecycline treatment.

Sensitivity:
The prevalence of acquired resistance may vary by geographic region and over time for certain species; therefore, it is very important to have local information on resistance, especially in the treatment of severe infections. The following information is an estimated guide for determining whether microorganisms will be susceptible to tigecycline:

Pathogen
Gram positive aerobes:
Enterococcus species[†] *Staphylococcus aureus** *Staphylococcus epidermidis* *Staphylococcus haemolyticus* *Streptococcus agalactiae** *Streptococcus anginosus** (including *S. anginosus, S. intermedius and S. constellatus)* *Streptococcus pyogenes** Viridans group streptococci
Gram negative aerobes
*Citrobacter freundii** *Citrobacter koseri* *Escherichia coli** *Klebsiella oxytoca**
Anaerobic bacteria
Clostridium perfringens[†] *Peptostreptococcus* spp.[†] *Prevotella* spp.
Species for which acquired resistance may be a problem
Gram negative aerobes *Acinetobacter baumannii* *Burkholderia cepacia* *Enterobacter aerogenes* *Enterobacter cloacae** *Klebsiella pneumoniae** *Morganella morganii* *Proteus spp.* *Providencia spp.* *Serratia marcescens* *Stenotrophomonas maltophilia* **Aerobes** *Bacteroides fragilis group*[†]
Hereditarily resistant organisms
Gram negative aerobes *Pseudomonas aeruginosa*

* Indicates the species whose activity demonstrated in clinical trials is judged to be satisfactory.

[†] See section 5.1, threshold values above.

Cardiac Electrophysiology

In a randomized, placebo and active, controlled four-arm crossover QTc study in 46 healthy volunteers, a single 50 mg or 200 mg intravenous dose of tigecycline had no significant effect on the QTc interval.

Pediatric population:
In an open-label, multiple-dose incremental study, 39 children aged 8 to 11 years with CIAE or cDYDE received tigecycline (0.75, 1, or 1.25 mg/kg). All patients received IV tigecycline for at least 3 consecutive days, with the option of switching to oral antibiotics on or after day 4, for a maximum of 14 consecutive days.
Clinical improvement was assessed 10 and 21 days after administration of the last dose.
A summary of clinical response in the modified intent-to-treat (mITT) population results is shown in the table below.

Clinical treatment / mITT population			
	0.75 mg/kg	1 mg/kg	1.25 mg/kg
Indication	n/N (%)	n/N (%)	n/N (%)
kİAE	6/6 (100.0)	3/6 (50.0)	10/12 (83.3)
kDYDE	3/4 (75.0)	5/7 (71.4)	2/4 (50.0)
General	9/10 (90.0)	8/13 (62.0%)	12/16 (75.0)

Since there were other antibiotics used concomitantly in this study, the efficacy data shown should be carefully examined. The small number of patients should also be taken into account.

Resistance
Resistance was rarely seen in strains determined to be susceptible to tigecycline in observational studies conducted in Europe. There was no development of cross-resistance between tigecycline and other antibiotics. Tigecycline has the ability to counteract ribosomal protection and efflux, which are two important resistance mechanisms for tetracycline. No antagonism was observed between tigecycline and other antibiotic classes in *in vitro* studies.

Clinical efficacy and safety
Complicated Skin and Skin Structure Infections:
The efficacy of tigecycline in the treatment of complicated skin and skin structure infections (cSCI) in adults was evaluated in two randomized, double-blind, active-controlled, multinational, and multicenter studies (studies 300 and 305). In these studies, Tigecycline (100 mg initial dose followed by 50 mg I.V. every 12 hours) administered for 5-14 days was compared with vancomycin (1 g I.V. every 12 hours)/aztreonam (2 g I.V. every 12 hours). These studies included patients with wound infections and complicated deep soft tissue infections such as cellulitis (≥10 cm, requiring surgical intervention/drainage or with underlying complicated disease), major abscesses, infected ulcers, and burns. The primary endpoint for efficacy was the clinical response rate in patients in the clinically evaluable group (CE-Clinically Evaluable) and clinically modified intent-to-treat group (c-mITT: clinical modified intent-to-treat) at the evaluation of improvement visit (TOC). *(see Table 1)*
The clinical improvement rate in TOC in patients who can be evaluated microbiologically is given in the table below.

Table 1: Complicated Skin and Skin Structure Infections
Clinical Response Rates After 5-14 Days of Treatment

	Tigecycline[a] n/N (%)	Vancomycin/ Aztreonam[b] n/N (%)
Study 300		
CE	165/199 (82.9)	163/198 (82.3)
c-mITT	209/277 (75.5)	200/260 (76.9)
Study 305		
CE	200/223 (89.7)	201/213 (94.4)
c-mITT	220/261 (84.3)	225/259 (86.9)

[a] 100 mg initially, then 50 mg every 12 hours
[b] Vancomycin (1 g I.V. every 12 hours) / Aztreonam (2 g I.V. every 12 hours)

Tigecycline did not meet the equivalence criteria in a comparative study with ertapenem in patients with diabetic foot infection.

Complicated Intra-abdominal Infections:
The efficacy of tigecycline in the treatment of complicated intra-abdominal infections (cIAE) in adults was evaluated in two randomized, double-blind, active-controlled, multinational, and multicenter studies (studies 301 and 306). In these studies, Tigecycline (100 mg initial dose followed by 50 mg IV every 12 hours) administered for 5-14 days was compared with imipenem/cilastatin (500 mg IV every 6 hours). Patients with complicated diagnoses such as appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, intra-abdominal abscess, bowel perforation and peritonitis were included in these studies. The primary efficacy endpoint was the clinical response in the microbiologically evaluable population (ME) and the microbiologically modified intent-to-treat population (m-mITT) at the evaluation of recovery visit (TOC). *(see., Table 2).* The clinical improvement rate in TOC in patients who can be evaluated microbiologically is given in the table below.

Table 2: Clinical Improvement Rates in Two Pivotal Studies Evaluating 5-14 Day
Treatment in Complicated Intra-abdominal Infections

	Tigecycline[a] n/N (%)	Imipenem/Cilastatin[b] n/N (%)
Study 301		
ME	199/247 (80.6)	210/255 (82.4)
m-mITT	227/309 (73.5)	244/312 (78.2)
Study 306		
ME	242/265 (91.3)	232/258 (89.9)
m-mITT	279/322 (86.6)	270/319 (84.6)

[a] 50 mg every 12 hours after an initial 100 mg dose
[b] Imipenem/Cilastatin (500 mg every 6 hours)

Community Acquired Bacterial Pneumonia
Tigecycline has been evaluated for the treatment of community-acquired bacterial pneumonia in two randomized, double-blind, active-controlled, multinational, multicenter studies in

adults (studies 308 and 313). In these studies, tigecycline (100 mg intravenous initial dose followed by 50 mg every 12 hours) was compared with levofloxacin (500 mg intravenous every 12 or 24 hours). In one study (study 308), conversion to oral levofloxacin (500 mg daily) was permitted in both treatment arms after at least 3 days of intravenous therapy. The total duration of treatment is 7-14 days. Studies included patients with community-acquired bacterial pneumonia requiring hospitalization and intravenous therapy. The primary efficacy endpoint is clinical response at visit (Test of Cure-TOC) where improvement is evaluated in co-primary populations of clinically evaluable (CE) and patients (c-mITT) who have received at least one clinically modified therapy drug (see Table of Materials). 2). The clinical improvement rates seen in TOC by pathogen in microbiologically evaluable patients are presented in Table 3.

Table 3: Clinical Recovery Rates After Total Treatment of 7-14 Days in Two Studies in Community-Acquired Bacterial Pneumonia

	Tigecycline[a] n/N (%)	Levofloxacin[b] n/N (%)	95% CI[c]
Study 308[d]			
CE	125/138 (90.6)	136/156 (87.2)	(-4.4, 11.2)
c-mITT	149/191 (78)	158/203 (77.8)	(-8.5, 8.9)
Çalışma 313			
CE	128/144 (88.9)	116/136 (85.3)	(-5.0, 12.2)
c-mITT	170/203 (83.7)	163/200 (81.5)	(-5.6, 10.1)

[a]100 mg initially, then 50 mg every 12 hours
[b]Levofloxacin (500 mg intravenous every 12 or 24 hours)
[c]95% confidence interval for difference between treatments
[d]After at least 3 days of intravenous therapy, switchover to oral levofloxacin (500 mg daily) was permitted in both treatment arms in study 308.

To further evaluate the efficacy of tigecycline, a post-hoc analysis was performed in patients with community-acquired bacterial pneumonia at high risk of mortality and with a history of antibiotic therapy. The high-risk group included patients in both studies with community-acquired bacterial pneumonia who had any of the following:

- Age ≥ 50
- PSI score ≥ 3
- *Streptococcus pneumoniae* pneumonia

The results of this analysis are shown in Table 4. The most common risk factor in the high-risk group is ≥ 50 years of age.

Table 4: Clinical Recovery Rates in Patients with Community-Acquired Bacterial Pneumonia Post-hoc Analysis by Mortality Risk[a]

	Tigecycline n/N (%)	Levofloxacin n/N (%)	%95 CI[b]
Study 308[c]			
CE			
High risk			
Exist	93/103 (90.3)	84/102 (82.4)	(-2.3, 18.2)

Not Exist	32/35 (91.4)	52/54 (96.3)	(-20.8, 7.1)
c-mITT			
High risk			
Exist	111/142 (78.2)	100/134 (74.6)	(-6.9, 14)
Not Exist	38/49 (77.6)	58/69 (84.1)	(-22.8, 8.7)
Study 313			
CE			
High risk			
Exist	95/107 (88.8)	68/85 (80)	(-2.2, 20.3)
Not Exist	33/37 (89.2)	48/51 (94.1)	(-21.1, 8.6)
c-mITT			
High risk			
Exist	112/134 (83.6)	93/120 (77.5)	(-4.2, 16.4)
Not Exist	58/69 (84.1)	70/80 (87.5)	(-16.2, 8.8)

[a] Patients at high risk of death include those who fit any of the following: age ≥50, PSI score ≥ 3, or bacteremia due to *Streptococcus pneumoniae*

[b] 95% confidence interval for difference between treatments

[c] After at least 3 days of intravenous therapy, switchover to oral levofloxacin (500 mg daily) was permitted in both treatment arms in study 308.

5.2. Pharmacokinetic Properties

General Features

Absorption:

Tigecycline is administered intravenously, so its bioavailability is 100%.

Distribution:

In vitro plasma protein binding of tigecycline at concentrations observed in clinical studies (0.1-1.0 µg/mL) averages between 71% and 89%. Animal and human studies have shown that tigecycline is rapidly distributed into tissues.

In rats given single or multiple doses of ^{14}C-tigecycline, it was observed that the radioactivity was well distributed to many tissues, and the regions with the highest uptake were bone, bone marrow, salivary glands, thyroid gland, spleen and kidneys. The steady-state volume of distribution of tigecycline in humans is on average 500-700 l (7-9 l/kg), indicating that tigecycline is widely distributed in tissues other than plasma in humans.

There are no data on the ability of tigecycline to cross the blood-brain barrier.

In a clinical pharmacology study in which 50 mg of tigecycline was given every 12 hours following an initial dose of 100 mg, the steady-state serum tigecycline C_{max} for a 30-minute infusion was 866±233 ng/ml, for a 60-minute infusion, the steady-state serum tigecycline C_{max} was 634±97 ng/ml. Steady-state AUC_{0-12hr} value is 2349±850 ng.hr/ml. The steady-state pharmacokinetic profile of tigecycline in specific tissues or body fluids in healthy subjects was studied in two separate studies. In a bronchoalveolar lavage study, the concentration under the curve (AUC_{0-12hr}) of tigecycline in alveolar cells was 134 µg.hr/ml, 78 times the serum AUC_{0-12hr} in these patients.

In the same study, AUC_{0-12hr} (2.28µg.hr/ml) in epithelial tissue fluid was found to be 32% higher than serum AUC_{0-12hr}. In a skin blister study, the AUC_{0-12hr} (1.61 µg.hr/ml) value in the

blister fluid was found to be approximately 26% below the serum $AUC_{0\text{-}12hr}$ values in these subjects.

In a single dose study, patients undergoing elective surgical or medical procedures for tissue extraction were given 100 mg I.V. tigecycline prior to this procedure. Concentration measurements were made in the following tissues 4 hours after the application: gallbladder, lung, colon, synovial fluid and bone. Tigecycline reached higher concentrations than serum in the gallbladder (38 times, 6 patients), lung (3.7 times 5 patients), and colon (2.3 times 6 patients). Concentrations of tigecycline after multiple doses have not been studied in these tissues.

Biotransformation:
On average, it is estimated that less than 20% of tigecycline is metabolized prior to excretion. In healthy male volunteers, the major 14C-labeled material detected in urine and faeces following 14C-tigecycline administration was tigecycline, but a glucuronide (N-acetyl metabolite) metabolite and tigecycline epimer are also available, each in amounts up to 10% of the administered dose. found.

In vitro studies with human liver microsomes have shown that metabolisms mediated by cytochrome P450 (CYP) isoforms 1A2, 2C8, 2C9, 2C19, 2D6 and 3A4 are not inhibited by competitive inhibition with tigecycline. In addition, tigecycline did not show dependence on NADPH in inhibition of CYP2C9, CYP2C19, CYP2D6 and CYP3A, which gave an idea about the absence of mechanism-based inhibition of CYP enzymes.

Elimination:
Detection of total radioactivity in urine and faeces after ^{14}C-tigecycline administration shows that 59% of the administered dose is excreted in the bile/feces and 33% in the urine. In general, the primary route and form of tigecycline is biliary excretion as unchanged tigecycline. Glucuronidation and urinary excretion of unchanged tigecycline are secondary pathways.

The total clearance of tigecycline is 24 L/h after intravenous infusion. Renal clearance is 13% of total clearance. Tigecycline shows polyexponential elimination with a mean terminal half-life from serum after multiple dosing of 42 hours, although interindividual variation is high.

According to an in vitro study using a P-gp overproducing cell line, tigecycline is a P-gp substrate. The potential contribution of P-gp-mediated transport to the in vivo trend of tigecycline is unknown. Concomitant use with P-gp inhibitors (eg ketoconazole or cyclosporine) or P-gp inducers (eg rifampicin) may affect the pharmacokinetics of tigecycline.

Linearity / nonlinearity:
TİGENEX shows linear pharmacokinetics.

Characteristics in patients

Hepatic Impairment:

The single-dose pharmacokinetics of tigecycline were unchanged in patients with mild hepatic impairment. In contrast, in patients with moderate hepatic impairment (Child Pugh B), the half-life of tigecycline was prolonged by 23% and systemic clearance was decreased by 25%. In addition, in patients with severe hepatic impairment (Child Pugh C), the half-life of tigecycline is prolonged by 43% and clearance is decreased by 55% (see section 4.2).

Renal Impairment:

Single dose pharmacokinetics of tigecycline were unchanged in patients with renal impairment (creatinine clearance < 30 mL/min, n=6). In severe renal impairment, AUC is increased by 30% compared to those with normal renal function.

Geriatric population:

No significant changes in pharmacokinetic properties were observed between healthy elderly subjects and young subjects.

Pediatric Patients:

The pharmacokinetics of tigecycline in patients aged 8-18 years have not been determined.
Tigecycline pharmacokinetics were investigated in 2 studies. The first study involved 8-16 years of age (n=24) who received a single dose of tigecycline (0.5, 1, or 2 mg/kg without dose limitation) intravenously over 30 minutes. The second study involved 8-11 years of age (n=47) who received multiple doses of tigecycline (0.75, 1, or 1.25 mg/kg, up to a maximum dose of 50 mg) intravenously every 12 hours for 30 minutes. Observed pharmacokinetic parameters are given below.

Dose mean ± SD tigecycline C_{max} and AUC normalized to 1 mg/kg in children			
Age (years)	N	C_{max} (ng/mL)	AUC (ng.hr/mL)
Single Dose			
8-11	8	3881 ± 6637	4034 ± 2874
12-16	16	8508 ± 11433	7026 ± 4088
Multiple Dose			
8-11	42	1911 ± 3032	2404 ± 1000

*Single dose $AUC_{0-\infty}$, Multiple dose EAA_{0-12hr}

The recommended 100 mg loading dose and 50 mg every 12 hours post-target AUC0-12s is approximately 2500 ng.hr/mL.

In the population PK analysis of both studies, body weight was defined as a covariate of tigecycline clearance in children 8 years of age and older.
Administration of tigecycline 1.2 mg/kg every 12 hours (maximum dose; 50 mg every 12 hours) in children aged 8 to 12 years and tigecycline 50 mg every 12 hours in adolescents aged 12 to 18 years, with those observed in adults treated with the approved dosing regimen. will result in comparable exposure. In these studies, higher C_{max} values were observed in many children than in adult patients.
In conclusion, attention should be paid to the infusion rate of tigecycline in children and adolescents.

Gender:
There was no clinically significant difference in the clearance of tigecycline between men and women. The AUC was estimated to be 20% higher in women than in men.

Race:
No race-related change was observed in the clearance of tigecycline.

Weight:
Clearance, weight-normalized clearance, and AUC were not significantly different in patients of different weights, including subjects with body weight ≥ 125 kg. AUC was 24% less in subjects with body weight ≥ 125 kg. No data are available for patients with a body weight ≥ 140 kg or more.

5.3. Pre-clinical safety data

In multiple dose toxicity studies in rats and dogs, based on AUC values in rats and dogs, tigecycline administration at doses 8.0 and 10.0 times the daily human dose, respectively, resulted in hypocellularity in the bone marrow and renal and gastrointestinal side effects, as well as lymphoid depletion / lymph nodes, spleen and thymus atrophy, erythrocyte atrophy. , reticulocyte, leukocyte and thrombocyte counts were decreased. These changes have been shown to be reversible after two weeks of dosing.

Bone discoloration has been observed in rats and is not reversible after two weeks of dosing.

According to the results of animal studies, tigecycline crossed the placenta and was found in fetal tissues. In reproductive toxicity studies, decreased fetal weight (related to delayed ossification) and fetal loss in rabbits were observed with tigecycline in rats and rabbits. Tigecycline is not teratogenic in rats or rabbits. Administration of tigecycline at doses 4.7 times the human daily dose based on AUC in rats did not affect mating or fertility.

Tigecycline is not teratogenic in rabbits and rats. In preclinical safety studies, 14C-labeled tigecycline has been proven to cross the placenta and is detected in fetal tissues (including fetal bone structure). Administration of tigecycline 5 times and 1 times the human daily dose (28 mcg.hr/mL and 6 mcg.hr/mL at 12 and 4 mg/kg/day, respectively) based on AUC in rats and rabbits, resulted in a slight decrease in fetal body weight in rats and rabbits, and An increased incidence of minor skeletal abnormalities (with a delay in bone formation) has been observed. An increased incidence of fetal loss was seen in rabbits at the maternatoxic dose when administered in doses equivalent to the human dose.

Animal studies using ^{14}C-labelled tigecycline have shown that tigecycline is excreted in milk in lactating rats. Consistent with the limited oral bioavailability of tigecycline, little or no systemic exposure to tigecycline was observed in breastfed offspring as a result of tigecycline's transfer into maternal milk.

Carcinogenicity
No long-term life-time animal studies have been conducted to determine the carcinogenic potential of tigecycline.

Mutagenicity
No mutagenic and clastogenic potential was observed in a series of tests, including in vitro chromosomal aberration assessment in Chinese hamster ovary cell (CHO), in vitro forward mutation assessment in CHO cells (HGRPT locus), in vitro forward mutation assessment in mouse lymphoma cells, and in vivo micronucleus assessments.

In animal studies, a histamine response has been observed with bolus I.V. administration of tigecycline. These effects occurred in rats and dogs, respectively, at doses 14 and 3 times the human daily doses.
No signs of photosensitivity were observed in rats after tigecycline administration.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients
Maltose monohydrate
Hydrochloric Acid
Water for injection

6.2. Incompatibilities
The following drugs should not be given concurrently with TİGENEX from the same set: Amphotericin B, amphotericin B liquid complex, diazepam, esomeprazole, omeprazole.
Suitable intravenous solutions are: 9mg/ml (0.9%) sodium chloride solution (USP), injection and 50mg/ml (5%) dextrose solution (USP) and Lactated Ringer's injection (USP) for injection. When TİGENEX is administered with 0.9% sodium chloride (USP) or 5% dextrose solution (USP), it can be given in the same set with the following drugs or solutions:
Amikacin, dobutamine, dopamine HCl, gentamicin, haloperidol, Lactated Ringer's solution, lidocaine HCl, metoclopramide, morphine, norepinephrine, piperacillin/tazobactam (EDTA formulation) potassium HCl, propofol, ranitidine HCl, theophylline, tobramycin.

6.3. Shelf Life
24 months

6.4. Special precautions for storage
Store at room temperature below 25ºC.
The reconstituted solution should be yellow-orange in color; If this color does not occur, the solution should not be used and discarded.
Once reconstituted, tigecycline can be stored at room temperature (25°C) for up to 24 hours (up to 6 hours in the vial, the remaining 18 hours in the IV bag).
Alternatively, tigecycline reconstituted solution mixed with 9 mg/ml (0.9%) sodium chloride solution for injection or 50 mg/ml (5%) dextrose solution for injection can be administered by I.V. It can be stored in the refrigerator at 2-8ºC for 48 hours after being transferred to the bag immediately.
Any unused solution should be discarded.

6.5. Nature and contents of container
5 ml Type I clear glass vial

It is presented in packages of 10 vials.

6.6. Special precautions for disposal and other handling

Administration instructions:
Tigecycline at a concentration of 10 mg/ml is obtained by mixing 5.3 ml of the powder with 9 mg/ml (0.9%) sodium chloride solution for injection or 50mg/ml (5%) dextrose solution for injection or Lactated Ringer's injection (USP). is done. The vial should be rotated slightly to allow the medicine to dissolve completely. Then, 5 ml of the immediately prepared solution is withdrawn from the vial and transferred to a 100 ml I.V. bag for infusion. For the 100 mg dose, 2 vials of medication should be prepared and transferred into a 100 ml I.V bag. (Note: There is an excess of 6% in the vial, so 5 ml of the prepared solution is equivalent to 50 mg of drug). **The prepared solution should be yellow-orange in color, otherwise the solution should not be used and discarded.** Parenteral products must be inspected for discoloration (eg green or black) and particulates prior to administration. Once reconstituted, it can be stored at room temperature for up to 24 hours (up to 6 hours in the vial, remaining time in the I.V. bag). Alternatively, tigecycline reconstituted solution mixed with 9 mg/ml (0.9%) sodium chloride solution for injection or 50 mg/ml (5%) dextrose solution for injection can be administered by I.V. It can be stored in the refrigerator at 2-8ºC for 48 hours after being transferred to the bag immediately.

TİGENEX can be administered alone on a separate I.V. line or on a common I.V. line. In cases where the same IV line is used for several drug infusions in a row, the vein line should be flushed with sodium chloride solution 9 mg/ml (0.9%) for injection or dextrose solution 5 mg/ml (5%) for injection before and after administration of TİGENEX. An infusion solution compatible with tigecycline should be used and care should be taken to ensure that the drug(s) administered through the same vascular line are compatible with tigecycline. *(see., section 6.2)*
Tigecycline is a broad-spectrum antibiotic used intravenously for the empiric treatment of moderate to severe bacterial infections. It does not directly pose a risk to the environment. Following approval, it will be distributed in EU countries and other European countries for application for injection. The main users of the product will be hospitals and clinics. The product will be presented in a vial. The packaging materials used are suitable for the distribution of this active substance, as explained in our dossier; It does not contain substances dangerous to health and environment.

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. MARKETING AUTHORIZATION HOLDER

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