For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

℞

Tigecycline for Injection USP 50mg

TIGEPLUG® टिजीप्लग

COMPOSITION
Each Vial contains:
Tigecycline USP 50 mg
Excipients q.s.
Sodium chloride Injection IP 5ml FFS Plastic Ampoule
Each mL contains:
Sodium chloride IP 9.0mg
Sterile water for Injections IP q.s.

PHARMACEUTICAL FORM
Lyophilized powder for reconstitution in a single-dose vial.
(For IV Use only)

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Antibacterials for systemic use
ATC code: J01AA12

Tigecycline is a tetracycline derivative (a glycylcycline) for intravenous infusion. The chemical name of tigecycline is (4S,4aS,5aR,12aS)-9-[2-(tert-butylamino)acetamido]-4,7bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide. The empirical formula is $C_{29}H_{39}N_5O_8$ and the molecular weight is 585.65.

Mechanism of Action
Tigecycline, a glycylcycline, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking the entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. Tigecycline carries a glycylamido moiety attached to the 9-position of minocycline.

Pharmacokinetic Properties
The mean pharmacokinetic parameters of tigecycline after single and multiple intravenous doses based on pooled data from clinical pharmacology studies are summarized in the below table. Intravenous infusions of tigecycline were administered over approximately 30 to 60 minutes.

Table 1: Mean Pharmacokinetic Parameters Of Tigecycline After Single And Multiple Intravenous Doses

	Single Dose 100 mg (N=224)	Multiple Dose[a] 50 mg q12h (N=103)
Cmax (µg/ml)[b]	1.45 (22%)	0.87 (27%)
Cmax (µg/ml)[c]	0.90 (30%)	0.63 (15%)
AUC (µg/ml)	5.19 (36%)	--
AUC 0-24h(µg/ml)	--	4.70 (36%)
Cmin (µg/ml)	--	0.13 (59%)
t1/2 (h)	27.1 (53%)	42.4 (83%)
CL (L/h)	21.8 (40%)	23.8 (33%)
CLr (ml/min)	38.0 (82%)	51.0 (58%)
Vss (L)	568 (43%)	639 (48%)

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] 30-minute infusion, [c] 60-minute infusion

The *in vitro* plasma protein binding of tigecycline ranges from approximately 71% to 89% at concentrations observed in clinical studies (0.1 to 1.0 µg/mL). Tigecycline is not extensively metabolized. Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline and its metabolites. Glucuronidation and renal excretion of unchanged tigecycline are secondary routes.

Clinical Studies
Complicated Skin and Skin Structure Infections
Tigecycline was evaluated in adults for the treatment of complicated skin and skin structure infections (cSSSI) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 300 and 305). These studies compared tigecycline (100 mg IV initial dose followed by 50 mg every 12 hours) with vancomycin (1g IV every 12 hours)/aztreonam (2 g IV every 12 hours) for 5 to 14 days. Patients with complicated deep soft tissue infections including wound infections and cellulitis (≥10 cm, requiring surgery/drainage or with complicated underlying disease), major abscesses, infected ulcers, and burns were enrolled in the studies. The primary efficacy endpoint was the clinical response at the test of cure (TOC) visit in the coprimary populations of the clinically evaluable (CE) and clinical modified intent-to-treat (cmITT) patients.

Table 2: Clinical Cure Rates from Two Pivotal Studies in Complicated Skin and Skin Structure Infections after 5 to 14 Days of Therapy

	Tigecycline[a] n/N (%)	Vancomycin/Aztreonam[b] n/N (%)
Integrated CE c-mITT	 365/422 (86.5) 429/538 (79.7)	 364/411 (88.6) 425/519 (81.9)
Study 300 CE c-mITT	 165/199 (82.9) 209/277 (75.5)	 163/198 (82.3) 200/260 (76.9)
Study 305 CE c-mITT	 200/223 (89.7) 220/261 (84.3)	 201/213 (94.4) 225/259 (86.9)

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] Vancomycin (1 g IV every 12 hours)/Aztreonam (2 g IV every 12 hours)

Table 3: Clinical Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Complicated Skin and Skin Structure Infections[a]

Pathogen	Tigecycline n/N (%)	Vancomycin/Aztreonam n/N (%)
Escherichia coli Enterococcus faecalis (vancomycin-susceptible only)	27/32 (84.4) 13/17 (76.5)	26/30 (86.7) 24/29 (82.8)
Methicillin-susceptible Staphylococcus aureus (MSSA)	125/139 (89.9)	118/126 (93.7)
Methicillin-resistant Staphylococcus aureus (MRSA)	29/37 (78.4)	26/34 (76.5)
Streptococcus agalactiae	8/8 (100)	11/13 (84.6)
Streptococcus anginosus grp.[b]	16/20 (80.0)	9/10 (90.0)
Streptococcus pyogenes	31/33 (93.9)	24/27 (88.9)
Bacteroides fragilis	6/8 (75.0)	4/5 (80.0)

[a] Two cSSSI pivotal studies and one Phase 3 Resistant Pathogen study
[b] Includes Streptococcus anginosus, Streptococcus intermedius, and Streptococcus constellatus

Complicated Intra-abdominal Infections
Tigecycline was evaluated in adults for the treatment of complicated intra-abdominal infections (cIAI) in two randomized, double-blind, active-controlled, multinational, multicenter studies (Studies 301 and 306). These studies compared tigecycline (100 mg IV initial dose followed by 50 mg every 12 hours) with imipenem/cilastatin (500 mg IV every 6 hours) for 5 to 14 days. Patients with complicated diagnoses including appendicitis, cholecystitis, diver ticulitis, gastric/duodenal perforation, intra-abdominal abscess, perforation of intestine, and peritonitis were enrolled in the studies. The primary efficacy endpoint was the clinical response at the TOC visit for the co-primary populations of the microbiologically evaluable (ME) and the microbiologic modified intent-to-treat (m-mITT) patients.

Table 4: Clinical Cure Rates from Two Pivotal Studies in Complicated Intra-abdominal Infections after 5 to 14 Days of Therapy

	Tigecycline[a] n/N(%)	Imipenem/Cilastatin[b] n/N(%)
integrated ME m-mITT	 441/512 (86.1) 506/631 (80.2)	 442/513 (86.2) 514/631 (81.5)
Study 301 ME m-mITT	 199/247 (80.6) 227/309 (73.5)	 210/255 (82.4) 244/312 (78.2)
Study 306 ME m-mITT	 242/265 (91.3) 279/322 (86.6)	 232/258 (89.9) 270/319 (84.6)

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] Imipenem/Cilastatin (500 mg every 6 hours)

Table 5: Clinical Cure Rates By Infecting Pathogen in Microbiologically Evaluable Patients with Complicated Intra-abdominal Infections[a]

Pathogen	Tigecycline n/N(%)	Imipenem/Cilastatin n/N(%)
Citrobacter freundii	12/16 (75.0)	3/4 (75.0)
Enterobacter cloacae	14/16 (87.5)	16/17 (94.1)
Escherichia coli	281/329 (85.4)	298/343 (86.9)
Klebsiella oxytoca	19/20 (95.0)	18/20 (90.0)
Klebsiella pneumoniae	46/52 (88.5)	53/60 (88.3)
Enterococcus faecalis (vancomycin-susceptible only)	25/33 (75.8)	35/47 (74.5)
Methicillin-susceptible		
Staphylococcus aureus (MSSA)	26/29 (89.7)	22/24 (91.7)
Streptococcus anginosus grp.[b]	102/120 (85.0)	61/81 (75.3)
Bacteroides fragilis	67/87 (77.0)	60/74 (81.1)
Bacteroides thetaiotaomicron	36/41 (87.8)	31/36 (86.1)
Bacteroides uniformis	12/17 (70.6)	14/17 (82.4)
Bacteroides vulgatus	14/16 (87.5)	5/7 (71.4)
Clostridium perfringens	19/20 (95.0)	20/22 (90.9)
Peptostreptococcus micros	14/18 (77.8)	9/12 (75.0)

[a] Two cIAI pivotal studies
[b] Includes Streptococcus anginosus, Streptococcus intermedius, and Streptococcus constellatus

Preclinical Safety Data
In repeated dose toxicity studies in rats and dogs, lymphoid depletion/atrophy of lymph nodes, spleen and thymus, decreased erythrocytes, reticulocytes, leukocytes, and platelets, in association with bone marrow hypocellularity, and adverse renal and gastrointestinal effects have been seen with tigecycline at exposures of 8 and 10 times the human daily dose based on AUC in rats and dogs, respectively. These alterations were shown to be reversible after two weeks of dosing.

Bone discoloring was observed in rats which was not reversible after two weeks of dosing.

Results of animal studies indicate that tigecycline crosses the placenta and is found in fetal tissues. In reproduction toxicity studies, decreased fetal weights in rats and rabbits (with associated delays in ossification) and fetal loss in rabbits have been observed with tigecycline. Tigecycline was not teratogenic in the rat or rabbit. Tigecycline did not affect mating or fertility in rats at exposures up to 4.7 times the human daily dose based on AUC. In female rats, there were no compound-related effects on ovaries or oestrus cycles at exposures up to 4.7 times the human daily dose based on AUC.

Results from animal studies using 14C-labelled tigecycline 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 the nursing pups as a result of exposure via maternal milk.

Lifetime studies in animals to evaluate the carcinogenic potential of tigecycline have not been performed, but short-term genotoxicity studies of tigecycline were negative.

Bolus intravenous administration of tigecycline has been associated with a histamine response in animal studies. These effects were observed at exposures of 14 and 3 times the human daily dose based on the AUC in rats and dogs respectively.

No evidence of photosensitivity was observed in rats following administration of tigecycline.

CLINICAL PARTICULARS
Therapeutic Indications
Complicated Skin and Skin Structure Infections
Complicated skin and skin structure infections caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin susceptible and resistant isolates), *Streptococcus agalactiae, Streptococcus anginosus* group (includes *S anginosus, S intermedius,* and *S constellatus*), *Streptococcus pyogenes,* and *Bacteroides fragilis.*

Complicated Intra-abdominal Infections
Complicated intra-abdominal infections caused by *Citrobacter freundii, Enterobacter cloacae, E. coli, Klebsiella oxytoca, K. pneumoniae, Enterococcus faecalis* (vancomycin susceptible isolates), *Staphylococcus aureus* (methicillin susceptible and resistant isolates), *Streptococcus anginosus* group (includes *S anginosus, S. intermedius, and S constellatus*), *Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens,* and *Peptostreptococcus micros.*

Tigecycline 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 tigecycline and other antibacterial drugs, it 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.

Posology and Method of Administration
The recommended dosage regimen for tigecycline is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous infusions (IV) of tigecycline should be administered over approximately 30 to 60 minutes every 12 hours.

The recommended duration of treatment with tigecycline 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 (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), 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 (Child Pugh C) should be treated with caution and monitored for treatment response.

No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing hemodialysis. No dosage adjustment of tigecycline is necessary based on age, gender, or race.

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.

Preparation and Handling
Each vial of TIGEPLUG should be reconstituted with 5ml of 0.9% sodium chloride injection IP or 5% Dextrose injection IP, to achieve a concentration of 10mg/ml of Tigecycline. The vial should be gently swirled until the drug dissolves. Withdraw entire content of the reconstituted solution from the vial and add to a 100ml intravenous bag for infusion (for a 100mg dose, reconstitute two vials, for a 50mg dose, reconstitute one vial). The maximum concentration in the intravenous bag should be 1mg/ml. The reconstituted solution should be yellow to orange in

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

℞

Tigecycline for Injection USP 50mg

TIGEPLUG® टिजीप्लग

colour, 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. If discoloured to green or black, then solution to be discarded. Once reconstituted, TIGEPLUG for injection may be stored at room temperature (Not exceeding 25°C/77°F) for upto 24 hrs (upto 6 hrs. in vial & remaining time in IV bag).

Alternatively, TIGEPLUG for injection may be stored refrigerated at 2 to 8°C (36° to 46°F)for up to 48 hours, following immediate transfer of reconstituted solution in to the IV bag. Reconstituted solution must be transferred & further diluted for IV infusion.

TIGEPLUG may be administered intravenously through a dedicated line or through 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 TIGEPLUG with 0.9% sodium chloride injection IP, 5% Dextrose injection IP. Injection should be made with an infusion solution compatible with Tigecycline and with any other drug administered via this common line.

Compatibilities
Compatible intravenous solutions include 0.9% Sodium Chloride Injection, IP, and 5% Dextrose Injection, IP. When administered through a Y-site, tigecycline is compatible with the following drugs or diluents: dobutamine, dopamine HCl, Lactated Ringer's, lidocaine HCl, potassium chloride, ranitidine HCl, and theophylline.

Incompatibilities
The following drugs should not be administered simultaneously through the same Y-site as tigecycline: amphotericin B, chlorpromazine, methylprednisolone, and voriconazole.

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

Special Warnings and Precautions for Use
Warnings
Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics and may have similar adverse effects.
Tigecycline may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking tigecycline, the patient should be apprised of the potential hazard to the fetus.

The use of tigecycline during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellowgray brown). Tigecycline should be administered with caution in patients with known hypersensitivity to tetracycline class antibiotics. Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Precautions
General
Caution should be exercised when considering tigecycline monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation.

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, pancreatitis, and anti-anabolic action (which has lead to increased BUN, azotemia, acidosis, and hypophosphatemia).

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.

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. 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 50mg 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 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.

Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.

Microbiology
Tigecycline, a glycylcycline, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains.

Tigecycline carries a glycylamido moiety attached to the 9-position of minocycline. The substitution pattern is not present in any naturally occurring or semisynthetic tetracycline and imparts certain microbiologic properties to tigecycline.

Tigecycline is not affected by the two major tetracycline resistance mechanisms, ribosomal protection and efflux. Accordingly, tigecycline has demonstrated *in vitro* and *in vivo* activity against a broad spectrum of bacterial pathogens. There has been no cross resistance observed between tigecycline and other antibiotics. Tigecycline is not affected by resistance mechanisms such as beta-lactamases (including extended spectrum beta-lactamases), target site modifications, macrolide efflux pumps or enzyme target changes (e.g. gyrase/topoisomerase).

Tigecycline has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections.

Aerobic facultative gram-positive microorganisms
Enterococcus faecalis (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius, and S. Constellatus*), *Streptococcus pyogenes.*

Aerobic and facultative gram-negative microorganisms
Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca.

Anaerobic microorganisms
Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens, Peptostreptococcus micros.

At least 90% of the following bacteria exhibit *in vitro* minimum inhibitory concentrations (MICs) that are at concentrations that are achievable using the prescribed dosing regimens. However, the clinical significance of this is unknown because the safety and effectiveness of tigecycline in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative gram-positive microorganisms
Enterococcus avium, Enterococcus casseliflavus, Enterococcus faecalis (vancomycin resistant isolates*), Enterococcus faecium (vancomycin-susceptible and resistant* isolates*), Enterococcus gallinarum, Listeria monocytogenes, Staphylococcus epidermidis* (methicillin susceptible and -resistant isolates) and *Staphylococcus haemolyticus.*
Aerobic and facultative gram-negative microorganisms
Acinetobacter baumannii, Aeromonas hydrophila, Citrobacter koseri, Enterobacter aerogenes, Pasteurella multocida, Serratiamarcescens and *Stenotrophomonas maltophilia.*
Anaerobic microorganisms
Bacteroides distasonis, Bacteroides ovatus, Peptostreptococcus spp., Porphyromonas spp., Prevotella spp.

Other microorganisms
Mycobacterium abscessus, Mycobacterium chelonae, Mycobacterium fortuitum

Pregnancy and Lactation
Pregnancy
There are no adequate and well-controlled studies of tigecycline in pregnant women. Tigecycline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
Because many drugs are excreted in human milk, caution should be exercised when tigecycline is administered to a nursing woman.

Effects on Ability to Drive and Use Machines
No studies on the effects of tigecycline on the ability to drive and use machines have been performed. Dizziness may occur and this may have an effect on driving and use of machines.

Undesirable Effects
The most common treatment-emergent adverse events, were nausea and vomiting which generally occurred during the first 1 – 2 days of 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.

Overdose
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 reported an increased incidence of nausea and vomiting. In single dose intravenous 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.

PHARMACEUTICAL PARTICULARS
Shelf Life
Please refer carton/label.

Storage and Precautions
Store at a temperature below 25°C. Protect from light.
Once reconstituted, tigecycline 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).

Keep out of reach of children.

Special Precautions for Disposal and Other Handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Nature and Contents of Container
TIGEPLUG® for injection is available in 10mL clear transparent glass vial, stoppered and sealed with flip off seal. One vial is packed with a 5mL FFS plastic ampoule of sodium chloride injection IP 0.9% w/v in a PVC tray, along with the package insert in a carton.

Pack size: 10mL vials

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

BrFLL/4007/01

Leaflet revised July 2020

To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free number: **1800 102 9465** or e-mail us at **drugsafety@biocon.com.**