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

Biocon

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Linezolid IV Injection 2mg/mL

ENTAVAR™ एन्टावर

COMPOSITION
Each 100 mL contains :
Linezolid IP 200 mg
Dextrose (Anhydrous) IP 5% w/v
Water for Injection IP qs to 100 mL

PHARMACEUTICAL FORM: Intravenous Injection
ATC Code: J01XX08

DESCRIPTION
ENTAVAR Injection contain Linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for Linezolid is (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide. The empirical formula is $C_{16}H_{20}FN_3O_4$. Its molecular weight is 337.35

CLINICAL PHARMACOLOGY
Pharmacokinetics
The mean pharmacokinetic parameters of Linezolid in adults after single and multiple intravenous (IV) doses are summarized in below table

Dose of Linezolid	C_{max} µg/mL	C_{min} µg/mL	T_{max} hrs	AUC* µg•h/mL	t1/2hrs	CL mL/min
600 mg IV injection single dose	12.90	--	0.50	80.20	4.40	138
every 12 hours	15.10	3.68	0.51	89.70	4.80	123

Absorption: Linezolid is rapidly and extensively absorbed after oral dosing. Maximum plasma concentrations are reached approximately 1 to 2 hours after dosing, and the absolute bioavailability is approximately 100%. Therefore, Linezolid may be given orally or intravenously without dose adjustment. Linezolid may be administered without regard to the timing of meals. The time to reach the maximum concentration is delayed from 1.5 hours to 2.2 hours and C_{max} is decreased by about 17% when high fat food is given with Linezolid. However, the total exposure measured as AUC0-∞ values is similar under both conditions.

Distribution: Animal and human pharmacokinetic studies have demonstrated that Linezolid readily distributes to well-perfused tissues. The plasma protein binding of Linezolid is approximately 31% and is concentration-independent. The volume of distribution of Linezolid at steady-state averaged 40 to 50 liters in healthy adult volunteers. Linezolid concentrations have been determined in various fluids from a limited number of subjects in Phase 1 volunteer studies following multiple dosing of Linezolid. The ratio of Linezolid in saliva relative to plasma was 1.2 to 1 and for sweat relative to plasma was 0.55 to 1.

Metabolism: Linezolid is primarily metabolized by oxidation of the morpholine ring, which results in two inactive ring-opened carboxylic acid metabolites: the aminoethoxyacetic acid metabolite (A), and the hydroxyethyl glycine metabolite (B). Formation of metabolite A is presumed to be formed via an enzymatic pathway whereas metabolite B is mediated by a non-enzymatic chemical oxidation mechanism in vitro. In vitro studies have demonstrated that Linezolid is minimally metabolized and may be mediated by human cytochrome P450. However, the metabolic pathway of Linezolid is not fully understood.

Excretion: Nonrenal clearance accounts for approximately 65% of the total clearance of Linezolid. Under steady-state conditions, approximately 30% of the dose appears in the urine as Linezolid, 40% as metabolite B, and 10% as metabolite A. The renal clearance of Linezolid is low (average 40 mL/min) and suggests net tubular reabsorption. Virtually no Linezolid appears in the feces, while approximately 6% of the dose appears in the feces as metabolite B, and 3% as metabolite A.

A small degree of nonlinearity in clearance was observed with increasing doses of Linezolid, which appears to be due to lower renal and nonrenal clearance of Linezolid at higher concentrations. However, the difference in clearance was small and was not reflected in the apparent elimination half-life.

Special Populations
Geriatric: The pharmacokinetics of Linezolid are not significantly altered in elderly patients (65 years or older). Therefore, dose adjustment for geriatric patients is not necessary.

Pediatric: The pharmacokinetics of Linezolid following a single IV dose were investigated in pediatric patients ranging in age from birth through 17 years (including premature and full-term neonates), in healthy adolescent subjects ranging in age from 12 through 17 years, and in pediatric patients ranging in age from 1 week through 12 years.

The C_{max} and the volume of distribution (Vss) of Linezolid are similar regardless of age in pediatric patients. However, clearance of Linezolid varies as a function of age. With the exclusion of pre-term neonates less than one week of age, clearance is most rapid in the youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric patients increases, the clearance of Linezolid gradually decreases, and by adolescence mean clearance values approach those observed for the adult population. There is wider inter-subject variability in Linezolid clearance and systemic drug exposure (AUC) across all pediatric age groups as compared with adults.

Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed every 8 hours (q8h) relative to adolescents or adults dosed every 12 hours (q12h). Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h.

Gender: Females have a slightly lower volume of distribution of Linezolid than males. Plasma concentrations are higher in females than in males, which is partly due to body weight differences. However, there are no significant gender differences in mean apparent elimination-rate constant or half-life. Thus, drug exposure in females is not expected to substantially increase beyond levels known to be well tolerated. Therefore, dose adjustment by gender does not appear to be necessary.

Renal Insufficiency: The pharmacokinetics of the parent drug, Linezolid, are not altered in patients with any degree of renal insufficiency; however, the two primary metabolites of Linezolid may accumulate in patients with renal insufficiency, with the amount of accumulation increasing with the severity of renal dysfunction. The clinical significance of accumulation of these two metabolites has not been determined in patients with severe renal insufficiency. Because similar plasma concentrations of Linezolid are achieved regardless of renal function, no dose adjustment is recommended for patients with renal insufficiency. However, given the absence of information on the clinical significance of accumulation of the primary metabolites, use of Linezolid in patients with renal insufficiency should be weighed against the potential risks of accumulation of these metabolites. Both Linezolid and the two metabolites are eliminated by dialysis. No information is available on the effect of peritoneal dialysis on the pharmacokinetics of Linezolid. Approximately 30% of a dose was eliminated in a 3-hour dialysis session beginning 3 hours after the dose of Linezolid was administered; therefore, Linezolid should be given after hemodialysis.
Hepatic Insufficiency: The pharmacokinetics of Linezolid are not altered in patients with mild-to-moderate hepatic insufficiency (Child-Pugh class A or B). On the basis of the available information, no dose adjustment is recommended for patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of Linezolid in patients with severe hepatic insufficiency have not been evaluated.

MICROBIOLOGY
Linezolid is a synthetic antibacterial agent of a new class of antibiotics, the oxazolidinones, which has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. The in vitro spectrum of activity of Linezolid also includes certain Gram-negative bacteria and anaerobic bacteria. Linezolid inhibits bacterial protein synthesis through a mechanism of action different from that of other antibacterial agents; therefore, cross-resistance between Linezolid and other classes of antibiotics is unlikely. Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process. The results of time-kill studies have shown Linezolid to be bacteriostatic against enterococci and staphylococci. For streptococci, Linezolid was found to be bactericidal for the majority of strains.

Linezolid has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections, as described in the INDICATIONS AND USAGE section.

Aerobic and facultative Gram-positive microorganisms
Enterococcus faecium (vancomycin-resistant strains only) Staphylococcus aureus (including methicillin-resistant strains) Streptococcus agalactiae, Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP]) Streptococcus pyogenes.

The following in vitro data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for Linezolid. However, the safety and effectiveness of Linezolid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative Gram-positive microorganisms
Enterococcus faecalis (including vancomycin-resistant strains) Enterococcus faecium (vancomycin-susceptible strains) Staphylococcus epidermidis (including methicillin-resistant strains) Staphylococcus haemolyticus
Viridans group streptococci.

Aerobic and facultative Gram-negative microorganisms
Pasteurella multocida

INDICATIONS AND USAGE
ENTAVAR formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms. Linezolid is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected.

Vancomycin-Resistant Enterococcus faecium infections, including cases with concurrent bacteremia. **Nosocomial pneumonia** caused by Staphylococcus aureus (methicillin-susceptible and resistant strains), or Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP]).

Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis, caused by Staphylococcus aureus (methicillin-susceptible and resistant strains), Streptococcus pyogenes, or Streptococcus agalactiae.

Uncomplicated skin and skin structure infections caused by Staphylococcus aureus (methicillin-susceptible only) or Streptococcus pyogenes.

Community-acquired pneumonia caused by Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP]), including cases with concurrent bacteremia, or Staphylococcus aureus (methicillin-susceptible strains only).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ENTAVAR and other antibacterial drugs, ENTAVAR should be used only to treat or prevent 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.

CONTRAINDICATIONS
ENTAVAR formulations are contraindicated for use in patients who have known hypersensitivity to Linezolid or any of the other product components.

Monoamine Oxidase Inhibitors Linezolid should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g., phenelzine, isocarboxazid) or within two weeks of taking any such medicinal product.

Potential Interactions Producing Elevation of Blood Pressure Unless patients are monitored for potential increases in blood pressure, Linezolid should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g., pseudoephedrine), vasopressive agents (e.g., epinephrine, norepinephrine), dopaminergic agents (e.g., dopamine, dobutamine) .

Potential Serotonergic Interactions Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, Linezolid should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine or buspirone.

WARNINGS

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving Linezolid. In cases where the outcome is known, when Linezolid was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive Linezolid, particularly in those who receive Linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with Linezolid should be considered in patients who develop or have worsening myelosuppression.

Linezolid is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections.

Linezolid has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ENTAVAR, and may range in severity from mild diarrhea to fatal colitis. CDAD must be considered in all patients who present with diarrhea following antibiotic use. 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
Lactic acidosis has been reported with the use of Linezolid. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving ENTAVAR should receive immediate medical evaluation.

Serotonin Syndrome :
Spontaneous reports of serotonin syndrome associated with the co-administration of ENTAVAR and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Where administration of ENTAVAR and concomitant serotonergic agents is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms).

Peripheral and optic neuropathy have been reported in patients treated with Linezolid, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with Linezolid for less than 28 days.

If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. **Visual function should be monitored in all patients taking ENTAVAR for extended periods (≥3 months) and in all patients reporting new visual symptoms regardless of length of therapy with ENTAVAR.** If peripheral or optic neuropathy occurs, the continued use of ENTAVAR in these patients should be weighed against the potential risks.

Convulsions have been reported in patients when treated with Linezolid. In some of these cases, a history of seizures or risk factors for seizures was reported.

The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.
Linezolid has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism.

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Prescribing ENTAVAR in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication 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 advised that:
- ENTAVAR may be taken with or without food.
- They should inform their physician if they have a history of hypertension.
- Large quantities of foods or beverages with high tyramine content should be avoided while taking ENTAVAR. Quantities of tyramine consumed should be less than 100 mg per meal.
- They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropanolamine HCl, such as cold remedies and decongestants.
- They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants.
- They should inform their physician if they experience changes in vision.
- They should inform their physician if they have a history of seizures.
- 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.

Patients should be counseled that antibacterial drugs including ENTAVAR should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold).

Drug-Drug Interactions
Drugs Metabolized by Cytochrome P450: Linezolid is not an inducer of cytochrome P450 (CYP450) in rats. In addition, Linezolid does not inhibit the activities of clinically significant human CYP isoforms. Therefore, Linezolid is not expected to affect the pharmacokinetics of other drugs metabolized by these major enzymes. Concurrent administration of Linezolid does not substantially alter the pharmacokinetic characteristics of (S)-warfarin, which is extensively metabolized by CYP2C9. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with Linezolid without changes in dosage regimen.

Antibiotics
Aztreonam: The pharmacokinetics of Linezolid or aztreonam are not altered when administered together.
Gentamicin: The pharmacokinetics of Linezolid or gentamicin are not altered when administered together.
Rifampin: The effect of rifampin on the pharmacokinetics of Linezolid was evaluated in a study of 16 healthy adult males. Volunteers were administered oral Linezolid 600 mg twice daily for 5 doses with and without rifampin 600 mg once daily for 8 days. Co¬administration of rifampin with Linezolid resulted in a 21% decrease in Linezolid C_{max} and a 32% decrease in Linezolid AUC_{0-12} .The mechanism of this interaction is not fully understood and may be related to the induction of hepatic enzymes.

Monoamine Oxidase Inhibition: Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, Linezolid has the potential for interaction with adrenergic and serotonergic agents.

Adrenergic Agents: A significant pressor response has been observed in normal adult subjects receiving Linezolid and tyramine doses of more than 100 mg. Therefore, patients receiving Linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content. A reversible enhancement of the pressor response of either pseudoephedrine HCl (PSE) or phenylpropanolamine HCl (PPA) is observed when Linezolid is administered to healthy normotensive.

Serotonergic Agents: The potential drug-drug interaction with dextromethorphan was studied in healthy volunteers. Subjects were administered dextromethorphan (two 20-mg doses given 4 hours apart) with or without Linezolid. No serotonin syndrome effects (confusion, delirium, restlessness, tremors, blushing, diaphoresis, hyperpyrexia) have been observed in normal subjects receiving Linezolid and dextromethorphan.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Lifetime studies in animals have not been conducted to evaluate the carcinogenic potential of Linezolid. Neither mutagenic nor clastogenic potential was found in a battery of tests including: assays for mutagenicity (Ames bacterial reversion and CHO cell mutation), an in vitro unscheduled DNA synthesis (UDS) assay, an in vitro chromosome aberration assay in human lymphocytes, and an in vivo mouse micronucleus assay.

Linezolid did not affect the fertility or reproductive performance of adult female rats. It reversibly decreased fertility and reproductive performance in adult male rats when given at doses ≥ 50 mg/kg/day, with exposures approximately equal to or greater than the expected human exposure level (exposure comparisons are based on AUCs). The reversible fertility effects were mediated through altered spermatogenesis. Affected spermatids contained abnormally formed and oriented mitochondria and were non-viable. Epithelial cell hypertrophy and hyperplasia in the epididymis was observed in conjunction with decreased fertility. Similar epididymal changes were not seen in dogs.

Pregnancy Teratogenic Effects. Pregnancy Category C: Linezolid was not teratogenic in mice, rats, or rabbits at exposure levels 6.5-fold (in mice), equivalent to (in rats), or 0.06-fold (in rabbits) the expected human exposure level, based on AUCs. However, embryo and fetal toxicities were seen there are no adequate and well-controlled studies in pregnant women. ENTAVAR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether Linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ENTAVAR is administered to a nursing woman.

Geriatric Use
No overall differences in safety or effectiveness were observed between these patients and younger patients.

ADVERSE REACTIONS
Adults
The most common adverse events in patients treated with Linezolid were diarrhea, headache nausea , insomnia, constipation, rash, dizziness, fever, oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, and tongue discoloration.

Pediatrics
Fever, diarrhea, vomiting, sepsis,rash, headache, anemia, thrombocytopenia, upper respiratory infection, nausea, dyspnea, reaction at site of infection, trauma, pharyngitis, convulsions.

DOSAGE AND ADMINISTRATION
The recommended dosage for ENTAVAR formulations for the treatment of infections is described in below table.

Infection*	Dosage and Route of Administration		Recommended Duration of Treatment (consecutive days)
	Pediatric Patients† (Birth through 11 Years of Age)	Adults and Adolescents (12 Years and Older)	
Complicated skin and skin structure infections Community-acquired pneumonia, including concurrent bacteremia Nosocomial pneumonia	10 mg/kg IV q8h	600 mg/kg IVq12h	10 to 14
Vancomycin-resistant *Enterococus faecium* infections, including concurrent bacteremia	10 mg/kg IV q8h	600 mg/kg IV q12h	14 to28
Uncomplicated skin and skin structure infections	<5yrs:10 mg/kg IVq8h 5-11yrs:600 mg/kg IVq12h	Adults:400 mg/kg IVq12h Adolescents:600 mg/kg IVq12h	10 to 14

*Due to the designated pathogens
† Neonates <7 days: Most pre-term neonates < 7 days of age (gestational age < 34 weeks) have lower systemic Linezolid clearance values and larger AUC values than many full-term neonates and older infants. These neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life

Adult patients with infection due to MRSA should be treated with ENTAVAR 600 mg q12h.
No dose adjustment is necessary when switching from intravenous to oral administration. Patients whose therapy is started with ENTAVAR I.V. Injection may be switched to either ENTAVAR Tablets at the discretion of the physician, when clinically indicated.

OVERDOSAGE
In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of Linezolid. In a Phase 1 clinical trial, approximately 30% of a dose of Linezolid was removed during a 3-hour hemodialysis session beginning 3 hours after the dose of Linezolid was administered. Data are not available for removal of Linezolid with peritoneal dialysis or hemoperfusion. Clinical signs of acute toxicity in animals were decreased activity and ataxia in rats and vomiting and tremors in dogs treated with 3000 mg/kg/day and 2000 mg/kg/day, respectively

Intravenous Administration
ENTAVAR I.V. Injection is supplied in single-use, ready-to-use infusion bottles. Parenteral drug products should be inspected visually for particulate matter prior to administration.

ENTAVAR I.V. Injection should be administered by intravenous infusion over a period of 30 to 120 minutes. Additives should not be introduced into this solution. If ENTAVAR I.V. Injection is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each product. In particular, physical incompatibilities resulted when Linezolid I.V. Injection was combined with the following drugs during simulated Y-site administration: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isothionate, erythromycin lactobionate, phenytoin sodium, and trimethoprim-sulfamethoxazole. Additionally, chemical incompatibility resulted when ENTAVAR I.V. Injection was combined with ceftriaxone sodium.

If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of ENTAVAR I.V. Injection with an infusion solution compatible with ENTAVAR I.V. Injection and with any other drug(s) administered via this common line
Store at room temperature. Protect from freezing. ENTAVAR I.V. Injection may exhibit a yellow color that can intensify over time without adversely affecting potency.

HOW SUPPLIED
ENTAVAR I.V. Injection is available in single-use, ready-to-use plastic bottles of 300ml in a foil laminate overwrap.

Shelf Life: Please refer carton/label.

Storage of ENTAVAR Formulations
Store protected from light and moisture, at a temperature not exceeding 30°C.
Keep out of reach of children.
Do not use the bottle if aluminium pouch is missing or tampered. Linezolid IV injection may exhibit a clear colourless to slightly brown or yellowish brown colour that can intensify over time without adversely affecting potency.

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
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Leaflet revised on August 2019

To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free No.: **1800 102 9465** or e mail us at **drugsafety@biocon.com**

BF/LL/3878/01

PI01861