1. NAME OF THE MEDICINAL PRODUCT

Metronidazole-Asteria Tab. 500mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient

No.	Chemical Name	Quantity/g	Use
1	Metronidazole	500mg	Active ingredient

Excipient(s)

No.	Chemical Name	Quantity/Tab.	Use
1	Magnesium stearate	5.0mg	Lubricant
2	Sodium carboxylmethylstarch	5.0mg	Disintegrant
3	20% starch dextrin	36mg	Adherent
4	Pregelatinized starch	20 mg	Diluent/Dinstegrant

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic Trichomoniasis: Metronidazole is indicated for the treatment of symptomatic trichomoniasis in females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures).

Asymptomatic Trichomoniasis: Metronidazole is indicated in the treatment of asymptomatic females when the organism is associated with endocervicitis, cervicitis, or cervical erosion. Since there is evidence that presence of the trichomonad can interfere with accurate assessment of abnormal cytological smears, additional smears should be performed after eradication of the parasite.

Treatment of Asymptomatic Consorts: T. vaginalis infection is a venereal disease. Therefore, asymptomatic sexual partners of treated patients should be treated simultaneously if the organism has been found to be present, in the order to prevent reinfection of the partner. The decision as to whether to treat an asymptomatic male partner who has a negative culture or one for whom no culture has been attempted is an individual one. In making this decision, it should be noted that there is evidence that a woman may become reinfected if her consort is not treated. Also, since there can be considerable difficulty in isolating the organism from the asymptomatic male carrier, negative smears and cultures cannot be relied upon in this regard. In any event, the consort should be treated with Metronidazole in cases of reinfection.

Amebiasis: Metronidazole is indicated in the treatment of acute intestinal amebiasis (amebic dysentery and amebic liver abscess.

In amebic liver abscess. Metronidazole therapy does not obviate the need for aspiration or drainage of pus.

Anaerobic Bacterial Infections: Metronidazole is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria. Indicated surgical procedures should be performed in conjunction with Metronidazole therapy. In a mixed aerobic and anaerobic infection, antibiotics appropriate for the treatment of the aerobic infection should be used in addition to Metronidazole.

In the treatment of most serious anaerobic infections, Metronidazole IV RTU (metronidazole) is usually administered initially. This may be followed by oral therapy with Metronidazole at the discretion of the physician.

Intra-Abdominal Infections, including peritonitis, intra-abdominal abscess, and liver abscess, caused by Bacteroides species including the B. fragilis group (B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus), Clostridium species, Eubacterium species, Peptococcus species, and Peptostreptococcus species.

Skin and Skin Structure Infections caused by Bacteroides species including the B. fragilis group, Clostridium species, Peptococcus species, Peptostreptococcus species, and Fusobacterium species.

Gynecological Infections, including endometritis, endomyometritis, tubo-ovarian abscess, and postsurgical vaginal cuff infection, caused by Bacteroides species including the B. fragilis group, Clostridium species, Peptococcus species, and Peptostreptococcus species.

Bacterial Septicemia caused by Bacteroides species including the B. fragilis group, and Clostridium species.

Bone and Joint Infections, as adjunctive therapy, caused by Bacteroides species including the B. fragilis group.

Central Nervous System (CNS) Infections, including meningitis and brain abscess, caused by Bacteroides species including the B. fragilis group.

Lower Respiratory Tract Infections, including pneumonia, empyema, and lung abscess, caused by Bacteroides species including the B. fragilis group.

Endocarditis caused by Bacteroides species including the B. fragilis group.

4.2 Posology and method of administration

In elderly patients the pharmacokinetics of metronidazole may be altered and therefore monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

Trichomoniasis

In the Female: *One-day treatment:* two grams of Metronidazole, given either as a single dose or in two divided doses of one gram each given in the same day. *Seven-day course of treatment:* 250 mg three times daily for seven consecutive days. There is some indication from controlled comparative studies that cure rates as determined by vaginal smears, signs and symptoms, may be higher after a seven-day course of treatment than after a one-day treatment regimen.

The dosage regimen should be individualized. Single-dose treatment can assure compliance, especially if administered under supervision, in those patients who cannot be relied on to continue the seven-day regimen. A seven-day course of treatment may minimize reinfection of the female long enough to treat sexual contacts. Further, some patients may tolerate one course of therapy better than the other.

Pregnant patients should not be treated during the first trimester with either regimen. If treated during the second or third trimester, the one-day course of therapy should not be used, as it results in higher serum levels which reach the fetal circulation.

When repeat courses of the drug are required, it is recommended that an interval of four to six weeks elapse between courses and that the presence of the trichomonad be reconfirmed by appropriate laboratory measures. Total and differential leukocyte counts should be made before and after re-treatment.

In the Male: Treatment should be individualized as for the female.

Amebiasis

Adults: *For acute intestinal amebiasis (acute amebic dysentery):* 750 mg orally three times daily for 5 to 10 days.

For amebic liver abscess: 500 mg or 750 mg orally three times daily for 5 to 10 days.

Children: 36 to 50 mg/kg/24 hours, divided into three doses, orally for 10 days.

Anaerobic Bacterial Infections

In the treatment of most serious anaerobic infections, Metronidazole HCl IV or Metronidazole IV RTU is usually administered initially.

The usual adult *oral* dosage is 7.5 mg/kg every six hours (approx. 500 mg for a 70-kg adult). A maximum of 4 g should not be exceeded during a 24-hours period.

The usual duration of therapy is 7 to 10 days; however, infections of the bone and joint, lower respiratory tract, and endocardium may require longer treatment.

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously. Close monitoring of plasma metronidazole levels[2] and toxicity is recommended.

The dose of Metronidazole should not be specifically reduced in anuric patients since accumulated metabolites may be rapidly removed by dialysis.

Store below 86°F (30°C) and protect from light.

4.3 Contraindications

Metronidazole is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

In patients with trichomoniasis, Metronidazole is contraindicated during the first trimester of pregnancy.

4.4 Special warnings and precautions

Warnings

Convulsive Seizures and Peripheral Neuropathy

Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with metronidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of Metronidazole therapy. Metronidazole should be administered with caution to patients with central nervous system diseases.

Precautions

General

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously.

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with Metronidazole and requires treatment with a candicidal agent.

Laboratory Tests

Metronidazole is a nitroimidazole and should be used with care in patients with evidence of or history of blood dyscrasia. A mild leukopenia has been observed during its administration; however, no persistent hematologic abnormalities attributable to metronidazole have been observed in clinical studies. Total and differential leukocyte counts are recommended before and after therapy for trichomoniasis and amebiasis, especially if a second course of therapy is necessary, and before and after therapy for anaerobic infection.

Drug/Laboratory Test Interactions

Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotine adenine dinucleotide (NAD^+<-> NADH). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Tumorigenicity studies in rodents: Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats.

Prominent among the effects in the mouse was pulmonary tumorigenesis. This has been observed in all six reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). At very high dose levels (approx. 500 mg/kg/day) there was statistically significant increase in the incidence of malignant liver tumors in males. Also, the published results of one of the mouse studies indicate an increase in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant.

Several long-term, oral-dosing studies in the rat have been completed. There were statistically significant increase in the incidence of various neoplasms, particularly in mammary and hepatic tumors, among female rats administered metronidazole over those noted in the concurrent female control groups.

Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Mutagenicity Studies

Although metronidazole has shown mutagenic activity in a number of *in vitro* assay systems, studies in mammals (*in vivo*) have failed to demonstrate a potential for genetic damage.

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

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when Metronidazole is prescribed for patients on this type of anticoagulant, therapy.

The simultaneous administration of drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.

The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole. In patients stabilized on relatively high doses of lithium, short-term Metronidazole therapy has been associated with elevation of serum lithium and in a few cases, signs of lithium toxicity. Serum lithium and serum creatinine levels should be obtained several days after beginning metronidazole to detect any increase that may precede clinical symptoms of lithium intoxication.

Alcoholic beverages should not be consumed during Metronidazole therapy and for at least one day afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur. Psychotic reactions have been reported in alcoholic patients who are using metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks.

4.6 Fertility, pregnancy and lactation

Pregnancy

Teratogenic Effects-Pregnancy Category B.

Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. Reproduction studies have been performed in rats at doses up to five times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to metronidazole. Metronidazole administered intraperitoneally to pregnant mice at approximately the human dose caused fetotoxicity; administered orally to pregnant mice, no fetotoxicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Because

animal reproduction studies are not always predictive of human response, and because metronidazole is a carcinogen in rodents, this drug should be used during pregnancy only if clearly needed.

Use of Metronidazole for trichomoniasis in the second and third trimesters should be restricted to those in whom local palliative treatment has been inadequate to control symptoms.

Nursing Mothers

Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Metronidazole is secreted in breast milk in concentrations similar to those found in plasma.

Pediatric Use

Safety and effectiveness in children have not been established, except for the treatment of amebiasis.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for drowsiness, dizziness, confusion, hallucinations, convulsions or transient visual disorders, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

Two serious adverse reactions reported in patients treated with Metronidazole have been convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged administration of Metronidazole, patients should be specifically warned about these reactions and should be told to stop the drug and report immediately to their physicians if any neurologic symptoms occur.

The most common adverse reactions reported have been referable to the gastrointestinal tract, particularly nausea reported by about 12% of patients, sometimes accompanied by headache,

anorexia, and occasionally vomiting; diarrhea; epigastric distress, and abdominal cramping. Constipation has been reported.

The following reactions have also been reported during treatment with Metronidazole:

Mouth: A sharp, unpleasant metallic taste is not unusual. Furry tongue, glossitis, and stomatitis have occurred; these may be associated with a sudden overgrowth of *Candida* which may occur during effective therapy.

Hematopoietic: Reversible neutropenia (leukopenia); rarely, reversible thrombocytopenia.

Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.

Central Nervous System: Convulsive seizures, peripheral neuropathy, dizziness, vertigo, incoordination, ataxia, confusion, irritability, depression, weakness, and insomnia.

Hypersensitivity: Urticaria, erythematous rash, flushing, nasal congestion, dryness of the mouth (or vagina or vulva), and fever.

Renal: Dysuria, cystitis, polyuria, incontinence, and a sense of pelvic pressure. Instances of darkened urine have been reported by approximately one patient in 100,000. Although the pigment which is which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.

Other: Proliferation of *Candida* in the vagina, dyspareunia, decrease of libido, proctitis, and fleeting joint pains sometimes resembling "serum sickness." If patients receiving Metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing, or headache. A modification of the taste of alcoholic beverages has also been reported. Rare cases of pancreatitis, which abated on withdrawal of the drug, have been reported.

Crohn's disease patients are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. There have been some reports in the medical literature of breast and colon cancer in Crohn’s disease patients who have been treated with metronidazole at high doses for extended periods of time. A cause and effect relationship has not been established. Crohn's disease is not an approved indication for Metronidazole.

4.9 Overdose

Single oral doses of metronidazole, up to 15 g, have been reported in suicide attempts and accidental overdoses. Symptoms reported include nausea, vomiting, and ataxia.

Oral metronidazole has been studies as a radiation sensitizer in the treatment of malignant tumors. Neurotoxic effects, including seizures and peripheral neuropathy, have been reported after 5 to 7 days of doses of 6 to 10.4 every other day.

Treatment: There is no specific antidote for Metronidazole overdose; therefore, management of the patient should consist of symptomatic and supportive therapy.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, ATC code: J01X D01

Metronidazole is active against a wide range of pathogenic micro-organisms notably species of *Bacteroides, Fusobacteria, Clostridia, Eubacteria, anaerobic cocci* and *Gardnerella vaginalis*. It is also active against *Trichomonas, Entamoeba histolytica, Giardia lamblia* and *Balantidium coli.*

5.2 Pharmacokinetic properties

[Pharmacokinetic evaluation of guar gum-based colon-targeted oral drug delivery systems of metronidazole in healthy volunteers.]

Eur J Drug Metab Pharmacokinet. 2003 Oct-Dec;28(4):287-94.

Krishnaiah YS, Veer Raju P, Dinesh Kumar B, Jayaram B, Rama B, Raju V, Bhaskar P.

Department of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530 003, India.

The present study was carried out to find the in vivo performance of guar gum-based colon-targeted tablets of metronidazole as compared to an immediate release tablets in human volunteers. Six healthy volunteers participated in the study and a crossover design was used. Blood samples were obtained at different time intervals and the plasma concentration of metronidazole was estimated by reverse phase HPLC. The immediate release tablets of metronidazole produced peak plasma concentration (C_{max} of 2990 +/- 574.6 ng/mL) within 2.8 +/- 0.6 h. On oral administration of colon-targeted tablets, metronidazole started appearing in the plasma between 5 h and 8 h, and reached the peak concentration (C_{max} of 1940.0 +/- 528.4 ng/mL) at 11.1 +/- 2.1 h (T_{max}). The AUC(0-infinity) and t(1/2) of metronidazole were unaltered on administering the drug as a colon-targeted tablet indicating that the extent of absorption and elimination were not affected by targeting the drug to the colon. However, colon-targeted tablets showed delayed T_{max} and absorption time (ta), decreased C_{max} and decreased absorption rate constant as compared to immediate release tablets. This in turn indicated that metronidazole was delivered to the colon resulting in a slow absorption of the drug and making it available for local action in the colon.

PMID: 14743970 [PubMed]

Bone Marrow Transplant. 2003 Mar;31(6):429-35

[The effect of metronidazole on busulfan pharmacokinetics in patients undergoing hematopoietic stem cell transplantation.]

Nilsson C, Aschan J, Hentschke P, Ringden O, Ljungman P, Hassan M.

Department of Medicine, Huddinge University Hospital, Stockholm, Sweden.

Busulfan (Bu) is an important component of some myeloablative regimens prior to stem cell transplantation (SCT). Over the last few years it has been shown that other drugs administered concomitantly can influence Bu pharmacokinetics. In the present study, we compared Bu concentrations (trough levels) in three groups of patients. Group A (n=5) received metronidazole as graft-versus-host disease prophylaxis during Bu treatment. Group B (n=9) received Bu only for 2 days followed by 2 days of Bu and metronidazole. Group C (n=10) was a control group that received Bu without metronidazole. The mean Bu levels for Group A receiving metronidazole during conditioning was significantly (P<0.001) higher (948+/-280 ng/ml), compared to those observed in the control group (507+/-75 ng/ml). In Group B, the administration of metronidazole resulted in a significant (P<0.001) increase in Bu levels (807+/-90 ng/ml) during the last 2 days, compared to 452+/-68 ng/ml during the first 2 days. In Group A, one patient died with multiorgan failure, three experienced veno-occlusive disease (VOD) and one developed hemorrhagic cystitis. Elevated liver transaminases (AST, ALT) and bilirubin were detected in all Group A patients. In Group B, six patients had elevated liver function tests but no VOD was observed. We conclude that metronidazole should not be administered simultaneously with Bu to avoid the high plasma levels of Bu, which may lead to severe toxicity and/or treatment related mortality

PMID: 12665836 [PubMed]

Hua Xi Kou Qiang Yi Xue Za Zhi. 1999 May;17(2):119-21.

[Evaluation of methods of drug release rate in root canal disinfection controlled-release delivery system containing metronidazole]

Wang Z, Wang D, Gao J, Zhang W.

Department of Stomatology, Shangdong Medical University.

OBJECTIVE: To measure the release rate of drug in controlled-release delivery system containing metronidazole. METHODS: Drug release tests in vitro, in vivo and through the roots of extracted teeth were performed. The release rate of metronidazole was calculated after 1 day, 3 days, 7 days and 10 days, and the results were statistically analyzed. RESULTS: Significant difference was observed among the total drug release rate in vitro, in vivo and through the roots of extracted teeth ($P < 0.01$). There was no statistically significant difference between the release test in vivo and through the roots of extracted teeth in vitro ($P > 0.05$). CONCLUSION: The method of using extracted teeth and the controlled release medium at 37 degrees C, pH7.4 was close to the situation in vivo, and it was an effective method to measure the drug release rate of the root canal disinfection controlled-release delivery system.

PMID: 12539701 [PubMed]

[Bioequivalence of a novel oral metronidazole formulation.]

The plasma pharmacokinetics of metronidazole (CAS 443-48-1) and its active OH-metabolite (CAS 4812-40-2) were investigated in 16 healthy volunteers after the oral administration of single oral doses of 500 mg metronidazole by means of a novel (test, T) and reference formulation (reference, R). The trial was conducted according to a randomised, controlled, open, within-subject cross-over design with two periods one week apart for wash-out. A single oral dose of 500 mg metronidazole by means of the test formulation T (Vagimid Dragees) resulted in a geometric mean C(max) of 10649 ng/ mL (CV: 0.21) for metronidazole after a median t(max) of 70 min (range: 40 to 120); the geometric mean of the AUC(0-t(z)) and AUC(0-infinity) were 107406 (CV: 0.25) and 109056 ng x h/mL (CV: 0.26); the arithmetic mean of the half-life (t1/2) and the mean residence time (MRT) were 7.28 h (CV: 0.12) and 11.62 h (CV: 0.10). For the OH-metabolite, the geometric mean C(max) was 1941 ng/mL (CV: 0.22) after a median t(max) of 480 min (range: 360 to 600) with a geometric mean AUC(0-tz) and AUC(0-infinity) of 48653 (CV: 0.21) and 52417 ng x h/mL (CV: 0.22), respectively; the arithmetic mean t1/2 and MRT were 10.60 h (CV: 0.21) and 21.14 h (CV: 0.13), respectively. The test formulation was bioequivalent with the reference formulation for both metronidazole (90% CI of the treatment ratio of 1.02 to 1.15 and 1.02 to 1.12 for C(max) and AUC) and its metabolite (90% CI of 0.92 to 1.05 and 0.98 to 1.06, respectively). The treatments were very well tolerated and there were no limiting safety-relevant findings.

PMID: 17009844 [PubMed - indexed for MEDLINE]

5.3 Preclinical safety data

Metronidazole has been shown to be carcinogenic in the mouse and in the rat following chronic oral administration however similar studies in the hamster have given negative results. Epidemiological studies have provided no clear evidence of an increased carcinogenic risk in humans.

Metronidazole has been shown to be mutagenic in bacteria in vitro. In studies conducted in mammalian cells in vitro as well as in rodent or humans in vivo, there was inadequate evidence of a mutagenic effect of metronidazole, with some studies reporting mutagenic effects, while other studies were negative.

6. PHARMACEUTICAL PARTICULARS

6.1 Excipients

No.	Chemical Name	Specification	Quantity/Tab.	Use
1	Magnesium stearate	USP	5.0mg	Lubricant
2	Sodium carboxylmethylstarch	KP	5.0mg	Disintegrant
3	20% starch dextrin	KP	36mg	Adherent
4	Pregelatinized starch	USP	20 mg	Diluent/Dinstegrant

6.2 Incompatibilities

None known

6.3 Shelf-life

3 years from manufacturing date

6.4 Special precautions for storage

Store in hermetic container at temperature below 25℃.

Protect from moisture.

Keep out of reach of children.

6.5 Nature and contents of container

10 tablets x 10 blisters / box

10 tablets x 3 blisters / box

6.5.1 Specifications and routine tests

1) Type

PVC sheet & Aluminum foil

2) Construction

- ALU / PVC blister

Trasparent colorless plastic film made of polyvinylchloride(PVC).

Aluminum foil with heat seal lacquer.

3) Quality specification (routine tests) and test procedures

Each immediate packaging material is tested according to the following testing instructions.

Plastic film PVC transparent colorless

Points tested	Test methods	Requirement
1. Outer packing	Visual control	Packing not damaged and/or badly contaminated
2. Total thickness	Checked with measuring device	x: 190 – 275 µm
3. Roll wrapping	Visual control	Not loosely wrapped or not too tightly wrapped
4. Mix-ups	Visual control	No mix-ups
5. Cleanliness	Visual control	Free of dust, fibres, dirt and insects
6. Colour	Visual control	Transparent colourless
7. Identity	PM-2071	Must qualitatively correspond to reference spectrum No. 006000
8. Permeability to +) moisture	PM-2061	Max. 1.2 g/m²/24h
9. Sealing seam strength	PM-2037 #)	Min. 7 N/15mm sealed against heat seal lacquer side of the corresponding counterfoil

Aluminum foil with heat seal lacquer

Points tested	Test methods	Requirement
1. Outer packing	Visual control	Packing not damaged and/ or badly contaminated
2. Total thickness	Checked with measuring device	x: 26 – 34 µm
3. Roll wrapping	Visual control	Not loosely wrapped or not too tightly wrapped
4. Mix-ups	Visual control	No mix-ups
5. Cleanliness	Visual control	Free of dust, fibres, dirt and insects
6. Identity of heat seal lacquer	PM-2071	Must qualitatively correspond to reference spectrum No. 080000
7. Sealing seam strength	PM-2037 #)	Min. 7 N/15 mm sealed against heat seal lacquer side of the corresponding counterfoil

6.5.2 Specifications and test methods

1) Specification

Materials examination and usage criteria:

Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Obsolete and outdated labels, labeling, and other packaging materials shall be destroyed.

Labeling issuance:

The "PASSED" label or printing should be issued.

Packaging and labeling operations:

Written procedures shall be followed. Results should be documented.

2) Testing Method

Materials examination and usage criteria:

Examine the condition of labeling and packaging materials. Labels and other labeling materials for each different drug product shall be stored separately. Printing should be monitoring.

Labeling issuance:

Strict control should be conducted before issuance.

The status of items will be indicated on the immediate container with a 'PASSED' sticker issued by Quality Assurance Department.

Packaging and labeling operations:

Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations.

Operate packaging and labeling. Record the results.

6.6 Special precautions for disposal and other handing

Not applicable

7. Manufacturer.

Hankook Korus Pharm. Co., Ltd.

30, Gangjeo-ro, Jecheon-si, Chungcheongbuk-do, Republic of Korea

7.1 Marketing authorization holder

Name :	GL Corporation
Address :	Woori Venture Tower #201, 70, Seonyu-ro, Yeongdeungpo-ku, Seoul, Republic of Korea
Tel :	+82 2 2675 7993
Fax :	+82 2 2675 7995

8. Marketing authorisation number(s)

N/A

9. Date of first authorisation/renewal of the authorisation

N/A

10. Date of revision of the text

September 18. 2015