SUMMARY PRODUCT CHARACTERISTICS

BIOTRIM DS TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Biotrim DS Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Biotrim DS tablet contains 800 mg Sulfamethoxazole and 160 mg of Trimethoprim.

Excipients,

For full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Tablet: White, caplet tablets with a break line on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Biotrim DS tablets are indicated for the treatment of the following infections when owing to sensitive organisms (see section 5.1):

Treatment and prevention of *Pneumocystis jiroveci (P. carinii)* pneumonitis.

Treatment and prophylaxis of toxoplasmosis Treatment

of nocardiosis.

The following infections may be treated with Biotrim where there is bacterial evidence of sensitivity to Biotrim and good reason to prefer the combination of antibiotics in Biotrim to a single antibiotic:

Acute uncomplicated urinary tract infection

Acute otitis media

Acute exacerbation of chronic bronchitis

Consideration should be given to official guidance on the appropriate use of antibacterial agents

4.2 Posology and method of administration

Method of administration: oral.

It may be preferable to take Biotrim with some food or drink to minimise the possibility of gastrointestinal disturbances.

Standard dosage recommendations for acute infections *Adults and children over 12 years:*

Tablets Standard Dose
1 every 12 hours

This dosage approximates to 6 mg trimethoprim and 30 mg sulfamethoxazole per kilogram body weight per 24 hours.

Treatment should be continued until the patient has been symptom free for two days; the majority will require treatment for at least 5 days. If clinical improvement is not evident after 7 days' therapy, the patient should be reassessed.

As an alternative to Standard Dosage for acute uncomplicated lower urinary tract infections, shortterm therapy of 1 to 3 days' duration has been shown to be effective.

The elderly:

See Special Warnings and Precautions for Use. Unless otherwise specified standard dosage applies.

Impaired hepatic function:

No data are available relating to dosage in patients with impaired hepatic function.

Special Dosage Recommendations

(Standard dosage applies unless otherwise specified).

Where dosage is expressed as "tablets" this refers to the adult tablet, i.e 80 mg Trimethoprim BP and 400 mg Sulfamethoxazole BP. If other formulations are to be used appropriate adjustment should be made.

Impaired renal function:

Adults and children over 12 years: (no information is available for children under 12 years of age).

Creatinine Clearance (ml/min)	Recommended Dosage
>30	STANDARD DOSAGE
15 to 30	Half the STANDARD DOSAGE
<15	Not recommended

Measurements of plasma concentration of sulfamethoxazole at intervals of 2 to 3 days are recommended in samples obtained 12 hours after administration of Biotrim. If the concentration of total sulfamethoxazole exceeds 150 microgram/ml then treatment should be interrupted until the value falls below 120 microgram/ml.

Pneumocystis jiroveci (P. carinii) pneumonitis: Treatment: A higher dosage is recommended using 20 mg trimethoprim and 100 mg sulfamethoxazole per kg of body weight per day in two or more divided doses for two weeks. The aim is to obtain peak plasma or serum levels of trimethoprim of

greater than or equal to 5 microgram/ml (verified in patients receiving 1-hour infusions of intravenous Biotrim). (See 4.8 Undesirable Effects).

Prevention: Adults: The following dose schedules may be used:

160 mg trimethoprim/800 mg sulfamethoxazole daily 7 days per week.

160 mg trimethoprim/800 mg sulfamethoxazole three times per week on alternative days. 320 mg trimethoprim/1600 mg sulfamethoxazole per day in two divided doses three times per week on alternative days.

Children:

The following dose schedules may be used for the duration of the period at risk (see Standard dosage recommendations for acute infections subsection of 4.2): - Standard dosage taken in two divided doses, seven days per week

- Standard dosage taken in two divided doses, three times per week on alternate days
- Standard dosage taken in two divided doses, three times per week on consecutive days
- Standard dosage taken as a single dose, three times per week on consecutive days

The daily dose given on a treatment day approximates to 150 mg trimethoprim/m^2/day and 750 mg sulfamethoxazole/m^2/day. The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole.

Nocardiosis: There is no consensus on the most appropriate dosage. Adult doses of 6 to 8 tablets daily for up to 3 months have been used (one tablet contains 400 mg sulfamethoxazole and 80 mg trimethoprim).

Toxoplasmosis: There is no consensus on the most appropriate dosage for the treatment or prophylaxis of this condition. The decision should be based on clinical experience. For prophylaxis, however, the dosages suggested for prevention of *Pneumocystis jiroveci* pneumonitis may be appropriate.

4.3 Contraindications

Biotrim should not be given to patients with a history of hypersensitivity to sulphonamides, trimethoprim, co-trimoxazole or any excipients of Biotrim.

Contra-indicated in patients showing marked liver parenchymal damage.

Contra-indicated in severe renal insufficiency where repeated measurements of the plasma concentration cannot be performed.

Biotrim should not be given to premature babies nor to full-term infants during the first 6 weeks of life except for the treatment/prophylaxis of PCP in infants 4 weeks of age or greater.

4.4 Special warnings and precautions for use

Fatalities, although very rare, have occurred due to severe reactions including fulminant hepatic necrosis, agranulocytosis, aplastic anaemia, other blood dyscrasias and hypersensitivity of the respiratory tract.

- Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Biotrim.
- Patients should be advised of the signs and symptoms and monitored closely for skin reactions.

The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

- If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Biotrim treatment should be discontinued (see 4.8 Undesirable Effects).
- The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.
- If the patient has developed SJS or TEN with the use of Biotrim, Biotrim must not be re-started in this patient at any time.

Particular care is always advisable when treating elderly patients because, as a group, they are more susceptible to adverse reactions and more likely to suffer serious effects as a result particularly when complicating conditions exist, e.g. impaired kidney and/or liver function and/or concomitant use of other drugs.

An adequate urinary output should be maintained at all times. Evidence of crystalluria *in vivo* is rare, although sulphonamide crystals have been noted in cooled urine from treated patients. In patients suffering from malnutrition the risk may be increased.

Regular monthly blood counts are advisable when Biotrim is given for long periods, or to folate deficient patients or to the elderly, since there exists a possibility of asymptomatic changes in haematological laboratory indices due to lack of available folate. These changes may be reversed by administration of folinic acid (5 to 10 mg/day) without interfering with the antibacterial activity.

In glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients haemolysis may occur.

Biotrim should be given with caution to patients with severe allergy or bronchial asthma. Biotrim should not be used in the treatment of streptococcal pharyngitis due to Group A betahaemolytic

streptococci; eradication of these organisms from the oropharynx is less effective than with penicillin.

Trimethoprim has been noted to impair phenylalanine metabolism but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

The administration of Biotrim to patients known or suspected to be at risk of acute porphyria should be avoided. Both trimethoprim and sulphonamides (although not specifically sulfamethoxazole) have been associated with clinical exacerbation of porphyria.

Close monitoring of serum potassium and sodium is warranted in patients at risk of hyperkalaemia and hyponatraemia.

Except under careful supervision Biotrim should not be given to patients with serious haematological disorders (see 4.8 Undesirable Effects). Biotrim has been given to patients receiving cytotoxic therapy with little or no additional effect on the bone marrow or peripheral blood.

The combination of antibiotics in Biotrim should only be used where, in the judgement of the physician, the benefits of treatment outweigh any possible risks; consideration should be given to the use of a single effective antibacterial agent.

4.5 Interaction with other medicinal products and other forms of interaction

Trimethoprim may interfere with the estimation of serum/plasma creatinine when the alkaline picrate reaction is used. This may result in overestimation of serum/plasma creatinine of the order of 10%. The creatinine clearance is reduced: the renal tubular secretion of creatinine is decreased from 23% to 9% whilst the glomerular filtration remains unchanged.

In some situations, concomitant treatment with zidovudine may increase the risk of haematological adverse reactions to co-trimoxazole. If concomitant treatment is necessary, consideration should be given to monitoring of haematological parameters.

Reversible deterioration in renal function has been observed in patients treated with cotrimoxazole and cyclosporin following renal transplantation.

Concurrent use of rifampicin and Biotrim results in a shortening of the plasma half-life of trimethoprim after a period of about one week. This is not thought to be of clinical significance.

When trimethoprim is administered simultaneously with drugs that form cations at physiological pH, and are also partly excreted by active renal secretion (e.g. procainamide, amantadine), there is

the possibility of competitive inhibition of this process which may lead to an increase in plasma concentration of one or both of the drugs.

In elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with or without purpura.

Occasional reports suggest that patients receiving pyrimethamine at doses in excess of 25 mg weekly may develop megaloblastic anaemia should co- trimoxazole be prescribed concurrently.

Co-trimoxazole has been shown to potentiate the anticoagulant activity of warfarin via stereoselective inhibition of its metabolism. Sulfamethoxazole may displace warfarin from plasmaalbumin protein-binding sites *in vitro*. Careful control of the anticoagulant therapy during treatment with Biotrim is advisable.

Co-trimoxazole prolongs the half-life of phenytoin and if co-administered could result in excessive phenytoin effect. Close monitoring of the patient's condition and serum phenytoin levels are advisable.

Concomitant use of trimethoprim with digoxin has been shown to increase plasma digoxin levels in a proportion of elderly patients.

Co-trimoxazole may increase the free plasma levels of methotrexate.

Trimethoprim interferes with assays for serum methotrexate when dihydrofolate reductase from *Lactobacillus casei* is used in the assay. No interference occurs if methotrexate is measured by radioimmuno assay.

Administration of trimethoprim/sulfamethoxazole 160mg/800mg (co- trimoxazole) causes a 40% increase in lamivudine exposure because of the trimethoprim component. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole.

Interaction with sulphonylurea hypoglycaemic agents is uncommon but potentiation has been reported.

Caution should be exercised in patients taking any other drugs that can cause hyperkalaemia. If Biotrim is considered appropriate therapy in patients receiving other anti- folate drugs such as methotrexate, a folate supplement should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are not any adequate data from the use of Biotrim in pregnant women. Case-control studies have shown that there may be an association between exposure to folate antagonists and birth defects in humans.

Trimethoprim is a folate antagonist and, in animal studies, both agents have been shown to cause foetal abnormalities (see 5.3 Preclinical Safety Data). Biotrim should not be used in pregnancy, particularly in the first trimester, unless clearly necessary. Folate supplementation should be considered if Biotrim is used in pregnancy.

Sulfamethoxazole competes with bilirubin for binding to plasma albumin. As significantly maternally derived drug levels persist for several days in the newborn, there may be a risk of precipitating or exacerbating neonatal hyperbilirubinaemia, with an associated theoretical risk of kernicterus, when Biotrim is administered to the mother near the time of delivery. This theoretical risk is particularly relevant in infants at increased risk of hyperbilirubinaemia, such as those who are preterm and those with glucose-6- phosphate dehydrogenase deficiency.

Lactation

The components of Biotrim (trimethoprim and sulfamethoxazole) are excreted in breast milk. Administration of Biotrim should be avoided in late pregnancy and in lactating mothers where the mother or infant has, or is at particular risk of developing, hyperbilirubinaemia. Additionally, administration of Biotrim should be avoided in infants younger than eight weeks in view of the predisposition of young infants to hyperbilirubinaemia.

4.7 Effects on ability to drive and use machines

There have been no studies to investigate the effect of Biotrim on driving performance or the ability to operate machinery. Further a detrimental effect on such activities cannot be predicted from the pharmacology of the drug. Nevertheless the clinical status of the patient and the adverse events profile of Biotrim should be borne in mind when considering the patients ability to operate machinery.

4.8 Undesirable effects

As co-trimoxazole contains trimethoprim and a sulphonamide the type and frequency of adverse reactions associated with such compounds are expected to be consistent with extensive historical experience.

Data from large published clinical trials were used to determine the frequency of very common to rare adverse events. Very rare adverse events were primarily determined from post-marketing experience data and therefore refer to reporting rate rather than a "true" frequency. In addition, adverse events may vary in their incidence depending on the indication.

The following convention has been used for the classification of adverse events in terms of frequency:- Very common ≥1/10, common ≥1/100 and <1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000. Infections and Infestations

Common: Monilial overgrowth

Blood and lymphatic system disorders

Very rare: Leucopenia, neutropenia, thrombocytopenia, agranulocytosis, megaloblastic anaemia, aplastic anaemia, haemolytic anaemia, methaemoglobinaemia, eosinophilia, purpura, haemolysis in certain susceptible G-6-PD deficient patients

Immune system disorders

Very rare: Serum sickness, anaphylaxis, allergic myocarditis, angioedema, drug fever, allergic vasculitis resembling Henoch-Schoenlein purpura, periarteritis nodosa, systemic lupus erythematosus

Metabolism and nutrition disorders

Very common: Hyperkalaemia

Very rare: Hypoglycaemia, hyponatraemia, anorexia

Psychiatric disorders

Very rare: Depression, hallucinations

Nervous system disorders

Common: Headache

Very rare: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, dizziness

Aseptic meningitis was rapidly reversible on withdrawal of the drug, but recurred in a number of cases on re-exposure to either co-trimoxazole or to trimethoprim alone.

Respiratory, thoracic and mediastinal disorders

Very rare: Cough, shortness of breath, pulmonary infiltrates

Cough, shortness of breath and pulmonary infiltrates may be early indicators of respiratory hypersensitivity which, while very rare, has been fatal. Gastrointestinal disorders

Common:	Nausea, diarrhoea
Uncommon:	Vomiting
Very rare: Eye Disorders	Glossitis, stomatitis, pseudomembranous colitis, pancreatitis
Very rare:	Uveitis

Hepatobiliary disorders

Very rare:	Elevation of serum transaminases, elevation of bilirubin levels, cholestatic jaundice, hepatic necrosis

Cholestatic jaundice and hepatic necrosis may be fatal. Skin and subcutaneous tissue disorders

Common:	Skin rashes
Very rare:	Photosensitivity, exfoliative dermatitis, fixed drug eruption, erythema multiforme, , severe cutaneous adverse reactions (SCARs): StevensJohnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4)

Musculoskeletal and connective tissue disorders

Very rare:	Arthralgia, myalgia

Renal and urinary disorders

Very rare:	Impaired renal function (sometimes reported as renal failure), interstitial nephritis

Effects associated with *Pneumocystis jiroveci (P.carinii)* Pneumonitis (PCP) management

Very rare:	Severe hypersensitivity reactions, rash, fever, neutropenia, thrombocytopenia, raised liver enzymes, hyperkalaemia, hyponatraemia, rhabdomyolysis.

At the high dosages used for PCP management severe hypersensitivity reactions have been reported, necessitating cessation of therapy. If signs of bone marrow depression occur, the patient should be given calcium folinate supplementation (5-10 mg/day). Severe hypersensitivity reactions have been reported in PCP patients on re-exposure to co-trimoxazole, sometimes after a dosage interval of a few days. Rhabdomyolysis has been reported in HIV positive patients receiving co-tromixazole for prophylaxis or treatment of PCP.

4.9 Overdose

Nausea, vomiting, dizziness and confusion are likely signs/symptoms of overdosage. Bone marrow depression has been reported in acute trimethoprim overdosage.

If vomiting has not occurred, induction of vomiting may be desirable. Gastric lavage may be useful, though absorption from the gastrointestinal tract is normally very rapid and complete within approximately two hours. This may not be the case in gross overdosage. Dependant on the status of renal function administration of fluids is recommended if urine output is low.

Both trimethoprim and active sulfamethoxazole are moderately dialysable by haemodialysis. Peritoneal dialysis is not effective.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of sulfonamides and trimethoprim, incl. derivatives;

ATC code: J01EE01

Mode of Action

Biotrim is an antibacterial drug composed of two active principles, sulfamethoxazole and trimethoprim. Sulfamethoxazole is a competitive inhibitor of dihydropteroate synthetase enzyme. Sulfamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid (PABA) in the synthesis of dihydrofolate by the bacterial cell resulting in bacteriostasis. Trimethoprim binds to and reversibly inhibits bacterial dihydrofolate reductase (DHFR) and blocks the production of tetrahydrofolate. Depending on the conditions the effect may be bactericidal. Thus trimethoprim and sulfamethoxazole block two consecutive steps in the biosynthesis of purines and therefore nucleic acids essential to many bacteria. This action produces marked potentiation of activity *in vitro* between the two agents.

Mechanism of resistance

In vitro studies have shown that bacterial resistance can develop more slowly with both sulfamethoxazole and trimethoprim in combination that with either sulfamethoxazole or trimethoprim alone.

Resistance to sulfamethoxazole may occur by different mechanisms. Bacterial mutations cause an increase the concentration of PABA and thereby out- compete with sulfamethoxazole resulting in a reduction of the inhibitory effect on dihydropteroate synthetase enzyme. Another resistance mechanism is plasmid-mediated and results from production of an altered dihydropteroate synthetase enzyme, with reduced affinity for sulfamethoxazole compared to the wild-type enzyme.

Resistance to trimethoprim occurs through a plasmid-mediated mutation which results in production of an altered dihydrofolate reductase enzyme having a reduced affinity for trimethoprim compared to the wild-type enzyme.

Trimethoprim binds to plasmodial DHFR but less tightly than to bacterial enzyme. Its affinity for mammalian DHFR is some 50,000 times less than for the corresponding bacterial enzyme.

Many common pathogenic bacteria are susceptible *in vitro* to trimethoprim and sulfamethoxazole at concentrations well below those reached in blood, tissue fluids and urine after the administration of recommended doses. In common with other antibiotics, however, *in vitro* activity does not necessarily imply that clinical efficacy has been demonstrated and it must be noted that satisfactory susceptibility testing is achieved only with recommended media free from inhibitory substances, especially thymidine and thymine.

Breakpoints

EUCAST

Enterobacteriaceae: S≤ 2 R> 4

S. maltophilia: S≤ 4 R> 4

Acinetobacter: S≤ 2 R> 4

Staphylococcus: S≤ 2 R> 4

Enterococcus: S≤ 0.032 R> 1

Streptococcus ABCG: S≤ 1 R> 2

Streptococcus pneumoniae: S≤ 1 R> 2

Hemophilus influenza: S≤ 0.5 R> 1

Moraxella catarrhalis: S≤0.5 R >1

Psuedomonas aeruginosa and other non-enterobacteriaceae: S≤ 2* R> 4*

S = susceptible, R = resistant. *These are CLSI breakpoints since no EUCAST breakpoints are currently available for these organisms.

Trimethoprim: sulfamethoxazole in the ratio 1:19. Breakpoints are expressed as trimethoprim concentration. Antibacterial Spectrum

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. This information gives only an approximate guidance on probabilities whether microorganisms will be susceptible to trimethoprim/sulfamethoxazole or not.

Trimethoprim/sulfamethoxazole susceptibility against a number of bacteria are shown in the table below:

Commonly susceptible species:
Gram-positive aerobes: *Staphylococcus aureus*

Staphylococcus saprophyticus *Streptococcus pyogenes*
Gram-negative aerobes:
Enterobacter cloacae *Haemophilus influenzae* *Klebsiella oxytoca Moraxella* *catarrhalis Salmonella* spp. *Stenotrophomonas maltophilia Yersinia* spp.
Species for which acquired resistance may be a problem:
Gram-positive aerobes: *Enterococcus faecalis* *Enterococcus faecium Nocardia* spp. *Staphylococcus epidermidis* *Streptococcus pneumoniae*

Gram-negative aerobes:
Citrobacter spp.
Enterobacter aerogenes
Escherichia coli
Klebsiella pneumoniae
Klebsiella pneumonia
Proteus mirabilis
Proteus vulgaris
Providencia spp.
Serratia marcesans
Inherently resistant organisms:
Gram-negative aerobes:
Pseudomonas aeruginosa
Shigella spp.
Vibrio cholera

5.2 Pharmacokinetic properties

After oral administration trimethoprim and sulfamethoxazole are rapidly and nearly completely absorbed. The presence of food does not appear to delay absorption. Peak levels in the blood occur between one and four hours after ingestion and the level attained is dose related. Effective levels persist in the blood for up to 24 hours after a therapeutic dose. Steady state levels in adults are reached after dosing for 2-3 days. Neither component has an appreciable effect on the concentrations achieved in the blood by the other.

Trimethoprim is a weak base with a pKa of 7.4. It is lipophilic. Tissue levels of trimethoprim are generally higher than corresponding plasma levels, the lungs and kidneys showing especially high concentrations. Trimethoprim concentrations exceed those in plasma in the case of bile, prostatic fluid and tissue, saliva, sputum and vaginal secretions. Levels in the aqueous humor, breast milk, cerebrospinal fluid, middle ear fluid, synovial fluid and tissue (intestinal) fluid are adequate for antibacterial activity. Trimethoprim passes into amniotic fluid and foetal tissues reaching concentrations approximating those of maternal serum.

Approximately 50% of trimethoprim in the plasma is protein bound. The half-life in man is in the range 8.6 to 17 hours in the presence of normal renal function. It is increased by a factor of 1.5 to 3.0 when the creatinine clearance is less than 10 ml/minute. There appears to be no significant difference in the elderly compared with young patients.

The principal route of excretion of trimethoprim is renal and approximately 50% of the dose is excreted in the urine within 24 hours as unchanged drug. Several metabolites have been identified in the urine. Urinary concentrations of trimethoprim vary widely..

Sulfamethoxazole is a weak acid with a pKa of 6.0. The concentration of active sulfamethoxazole in a variety of body fluids is of the order of 20 to 50% of the plasma concentration.

Approximately 66% of sulfamethoxazole in the plasma is protein bound. The half-life in man is approximately 9 to 11 hours in the presence of normal renal function.

There is no change in the half-life of active sulfamethoxazole with a reduction in renal function but there is prolongation of the half-life of the major, acetylated metabolite when the creatinine clearance is below 25ml/minute.

The principal route of excretion of sulfamethoxazole is renal; between 15% and 30% of the dose recovered in the urine is in the active form. In elderly patients there is a reduced renal clearance of sulfamethoxazole.

5.3 Preclinical safety data

Reproductive toxicology: At doses in excess of recommended human therapeutic dose, trimethoprim and sulfamethoxazole have been reported to cause cleft palate and other foetal abnormalities in rats, findings typical of a folate antagonist. Effects with trimethoprim were preventable by administration of dietary folate. In rabbits, foetal loss was seen at doses of trimethoprim in excess of human therapeutic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Starch BP
- Sodium Methyl Paraben BP
- Sodium Propyl Paraben BP
- Magnesium Stearate BP
- Gelatin BP

- Talc BP

6.2 Incompatibilities:

None known.

6.3 Shelf life:

3 years.

6.4 *Special precautions for storage:*

Do not store above 30°C

Store in the original package

6.5 Nature and contents of the container:

Pack sizes: Blister packed tablets in aluminum foils.

: 1000tablets in polythene bags packed in HDPE jars.

6.6 Special precautions for disposal:

No special requirements.

7. Registrant:

Biodeal Laboratories Limited,

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