BIORAJ PHARMACEUTICALS LIMITED	
BRAND NAME: KISTRIM SUSPENSION	**GENERIC NAME: CO-TRIMOXAZOLE B.P.(240mg)**
SUMMARY OF PRODUCT CHARACTERISTICS	

1. NAME OF THE MEDICINAL PRODUCT

Co-ttrimoxazole Suspension B.P. 240mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains: 40mg Trimethoprim BP. and 200mg Sulphamethoxazole BP.

3. PHARMACEUTICAL FORM

Suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-trimoxazole is indicated in adults and children (>12 to <18 years old) and adults (>18 years old).

Co-trimoxazole suspension are indicated for the treatment of the following infections when owing to sensitive organisms:

- Treatment and prevention of *Pneumocystis jiroveci* pneumonitis or 'PJP'.
- Treatment and prophylaxis of toxoplasmosis
- Treatment of nocardiosis.

The following infections may be treated with co-trimoxazole where there is bacterial evidence of sensitivity to co-trimoxazole and good reason to prefer the combination of antibiotics in co-trimoxazole 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

Posology

General Dosage Recommendations

Where dosage is expressed as "suspenion" this refers to the adult suspension, i.e. 40 mg Trimethoprim BP and 200 mg Sulphamethoxazole BP. If other formulations are to be used appropriate adjustment should be made.

Standard dosage recommendations for acute infections

The standard dosage for children is equivalent to approximately 6 mg trimethoprim and 30 mg sulphamethoxazole per kg body weight per day, given in two equally divided doses. The schedules for children are according to the child's age and provided below:

Children (6wks-5 months) - 2.5ml every 12 hours.

Children (6mnths -5yrs) - 5ml every 12 hours.

Children (6-12yrs) -10ml every 12 hours

For severe infections, dosage may be increased by 50%. Treatment should continue until the patient is symptoms free for two days, majority will require treatment for at least five days.

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

Elderly patients:

See Special Warnings and Precautions for Use (Section 4.4). Unless otherwise specified standard dosage applies.

Impaired hepatic function:

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

Impaired renal function:

Dosage recommendation:

Children (6wks-5 months) - 2.5ml every 12 hours.

Children (6mnths -5yrs) - 5ml every 12 hours.

Children (6-12yrs) -10ml every 12 hours

No information available for children aged 12 years and under with renal failure.

Measurements of plasma concentration of sulphamethoxazole at intervals of 2 to 3 days are recommended in samples obtained 12 hours after administration of Co-Trimoxazole.

If the concentration of total sulphamethoxazole exceeds 150 microgram/ml then treatment should be interrupted until the value falls below 120 microgram/ml.

Nocardiosis - Adults (>18 years old):

There is no consensus on the most appropriate dosage. Adult doses of 6 to 8 suspension daily for up to 3 months have been used.

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.

Method of administration:

Oral route.

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

4.3 Contraindications

Co-trimoxazole is contraindicated in patients who are hypersensitive to sulphonamides and trimethoprim, premature babies/neonates, end of pregnancy, lactation and patients deficient in glucose 6-phosphate dehydrogenase.

• Hypersensitivity to any of the excipients listed in section 6.1.

• Co-trimoxazole should not be given to patients with severe impairment of liver function.

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

• Co-trimoxazole should not be given to infants during the first 6 weeks of life.

• Co-trimoxazole should not be given to patients with a history of drug-induced immune thrombocytopenia with use of trimethoprim and/or sulfonamides.

• Co-trimoxazole should not be given to patients with acute porphyria.

4.4 Special warnings and precautions for use:

- If skin rash appears in the course of administration, please stop treatment and consult your physician.
- Administration to patients with renal impairment or acute porphyria should be avoided.
- Regular monthly blood count is necessary when administered for a long period.
- Specific laboratory monitoring must be carried out in hepatic inadequacy, an history of blood dyscrasia and renal insufficiency.
- Not recommended during pregnancy except in an emergency closely monitored by a physician.

Haemophagocytic lymphohistiocytosis (HLH)

Cases of HLH have been reported very rarely in patients treated with co-trimoxazole. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of an excessive systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis). Patients who develop early manifestations of pathologic immune activation should be evaluated immediately. If diagnosis of HLH is established, co-trimoxazole treatment should be discontinued.

Respiratory toxicity

Very rare, severe cases of respiratory toxicity, sometimes progressing to Acute Respiratory Distress Syndrome (ARDS), have been reported during co-trimoxazole treatment. The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function may be preliminary signs of ARDS. In such circumstances, co-trimoxazole should be discontinued and appropriate treatment given.

Elderly patients

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.

Patients with renal impairment

For patients with known renal impairment special measures should be adopted.

Urinary output

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

Folate

Regular monthly blood counts are advisable when co-trimoxazole 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. Supplementation with folinic acid may be considered during treatment but this should be initiated with caution due to possible interference with antimicrobial efficacy.

Patients with glucose-6-phosphate dehydrogenase deficiency

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

Patients with severe atopy or bronchial asthma

Co-trimoxazole should be given with caution to patients with severe atopy or bronchial asthma.

Treatment of streptococcal pharyngitis due to Group A beta-haemolytic streptococci

Co-trimoxazole should not be used in the treatment of streptococcal pharyngitis due to Group A beta-haemolytic *streptococci*; eradication of these organisms from the oropharynx is less effective than with penicillin.

Phenylalanine metabolism

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

Patients with or at risk of porphyria

The administration of co-trimoxazole to patients known or suspected to be at risk of acute porphyria should be avoided. Both trimethoprim and sulfonamides (although not specifically sulphamethoxazole) have been associated with clinical exacerbation of porphyria.

Patients with hyperkalaemia and hyponatraemia

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

Metabolic acidosis

Co-Trimoxazole has been associated with metabolic acidosis when other possible underlying causes have been excluded. Close monitoring is always advisable when metabolic acidosis is suspected.

Patients with serious haematological disorders

Except under careful supervision co-trimoxazole should not be given to patients with serious haematological disorder. Co-trimoxazole 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 co-trimoxazole 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.

Information on sodium content

This medicine contains less than 1 mmol sodium (23 mg) per suspension, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with laboratory tests: 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.

Zidovudine: 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.

Cyclosporin: reversible deterioration in renal function has been observed in patients treated with co-trimoxazole and cyclosporin following renal transplantation.

Rifampicin: concurrent use of rifampicin and Co-Trimoxazole 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.

Diuretics (thiazides): in elderly patients concurrently receiving diuretics, mainly thiazides, there appears to be an increased risk of thrombocytopenia with or without purpura.

Pyrimethamine: 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.

Warfarin: co-trimoxazole has been shown to potentiate the anticoagulant activity of warfarin via stereo-selective inhibition of its metabolism. Sulphamethoxazole may displace warfarin from plasma-albumin protein-binding sites *in vitro*. Careful control of the anticoagulant therapy during treatment with Co-Trimoxazole is advisable.

Phenytoin: 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.

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

Methotrexate: co-trimoxazole may increase the free plasma levels of methotrexate. If Co-Trimoxazole is considered appropriate therapy in patients receiving other anti- folate drugs such as methotrexate, a folate supplement should be considered (see section 4.4). 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.

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

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

Hyperkalaemia: caution should be exercised in patients taking any other drugs that can cause hyperkalaemia, for example ACE inhibitors, angiotensin receptor blockers and potassium-sparing diuretics such as spironolactone. Concomitant use of trimethoprim-sulphamethoxazole (co-trimoxazole) may result in clinically relevant hyperkalaemia.

Repaglinide: trimethoprim may increase the exposure of repaglinide which may result in hypoglycaemia.

Folinic acid: folinic acid supplementation has been shown to interfere with the antimicrobial efficacy of trimethoprim-sulphamethoxazole. This has been observed in *Pneumocystis jirovecii* pneumonia prophylaxis and treatment.

Contraceptives: oral contraceptive failures have been reported with antibiotics. The mechanism of this effect has not been elucidated. Women on treatment with antibiotics should temporarily use a barrier method in addition to the oral contraceptive, or choose another method of contraception.

Azathioprine: There are conflicting clinical reports of interactions between azathioprine and trimethoprim-sulphamethoxazole, resulting in serious haematological abnormalities.

4.6 Fertility, pregnancy and lactation

Pregnancy

Trimethoprim and sulphamethoxazole cross the placenta and their safety in pregnant women has not been established. 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 section 5.3).

Co-trimoxazole should not be used in pregnancy, particularly in the first trimester, unless clearly necessary. Folate supplementation should be considered if co-trimoxazole is used in pregnancy.

Sulphamethoxazole 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 co-trimoxazole 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.

Breast-feeding

The components of co-trimoxazole (trimethoprim and sulphamethoxazole) are excreted in breast milk. Administration of co-trimoxazole 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 co-trimoxazole 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 co-trimoxazole 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 co-trimoxazole should be borne in mind when considering the patient’s ability to operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The frequency categories associated with the adverse events below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse events may vary in their incidence depending on the indication.

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.

Tabulated list of adverse reaction

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, not known - cannot be estimated from the available data.

Description of selected adverse reactions

Aseptic meningitis: 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.

Pulmonary hypersensitivity reactions: Cough, dyspnoea and lung infiltration may be early indicators of respiratory hypersensitivity which, while very rare, has been fatal.

Hepatobiliary disorders: Jaundice cholestatic and hepatic necrosis may be fatal.

Severe cutaneous adverse reactions (SCARs) : Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported to be life-threatening.

As with any other drug, allergic reactions such as an itchy rash and hives may occur in patients with hypersensitivity to the components of the drug. Very rare cases of acute generalised exanthematous pustulosis (AGEP) have been observed.

Rhabdomyolysis: has been reported in HIV positive patients receiving co-trimoxazole for prophylaxis.

4.9 Overdose

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

Treatment: 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 sulphamethoxazole are moderately dialysable by haemodialysis. Peritoneal dialysis is not effective.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use - Sulfonamides and trimethoprim;

ATC code: J01EE01

Mechanism of Action

Co-trimoxazole is an antibacterial drug composed of two active principles, sulphamethoxazole and trimethoprim. Sulphamethoxazole is a competitive inhibitor of dihydropteroate synthetase enzyme. Sulphamethoxazole competitively inhibits the utilisation of para-aminobenzoic acid (PABA) in the synthesis of dihydrofolate by the bacterial cell resulting in bacteriostasis. Trimethoprim reversibly inhibits bacterial dihydrofolate reductase (DHFR), an enzyme active in the folate metabolic pathway converting dihydrofolate to tetrahydrofolate. Depending on the conditions the effect may be bactericidal. Thus trimethoprim and sulphamethoxazole 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.

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

Mechanism of resistance

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

Resistance to sulphamethoxazole may occur by different mechanisms. Bacterial mutations cause an increase the concentration of PABA and thereby out-compete with sulphamethoxazole 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 sulphamethoxazole 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 sulphamethoxazole 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.

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/sulphamethoxazole or not.

5.2 Pharmacokinetic properties

Absorption

After oral administration trimethoprim and sulphamethoxazole 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.

Distribution

Approximately 50% of trimethoprim in the plasma is protein bound.

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 66% of sulphamethoxazole in the plasma is protein bound. The concentration of active sulphamethoxazole in amniotic fluid, aqueous humour, bile, cerebrospinal fluid, middle ear fluid, sputum, synovial fluid and tissue (interstitial) fluids is of the order of 20 to 50% of the plasma concentration.

Biotransformation

Renal excretion of intact sulphamethoxazole accounts for 15-30% of the dose. This drug is more extensively metabolised than trimethoprim, via acetylation, oxidation or glucuronidation. Over a 72 hour period, approximately 85% of the dose can be accounted for in the urine as unchanged drug plus the major (N4-acetylated) metabolite.

Elimination

The half-life of trimethoprim 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 elderly patients 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.

The half-life of sulphamethoxazole 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 sulphamethoxazole 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 25 ml /minute.

The principal route of excretion of sulphamethoxazole is renal; between 15% and 30% of the dose recovered in the urine is in the active form.

The pharmacokinetics in the paediatric population with normal renal function of both components of Co-Trimoxazole, TMP and SMZ are age dependent. Elimination of TMP-SMZ is reduced in neonates, during the first two months of life, thereafter both TMP and SMZ show a higher elimination with a higher body clearance and a shorter elimination half-life. The differences are most prominent in young infants (> 1.7 months up to 24 months) and decrease with increasing age, as compared to young children (1 year up to 3.6 years), children (7.5 years and < 10 years) and adults (see section 4.2).

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.

In elderly patients there is a reduced renal clearance of sulphamethoxazole.

Special patient population

Renal impairment

The elimination half-life of trimethoprim is increased by a factor of 1.5-3.0 when the creatinine clearance is less than 10 mL/minute. When the creatinine clearance falls below 30 mL/min the dosage of Co-Trimoxazole should be reduced (see section 4.2).

Hepatic impairment

Caution should be exercised when treating patients with severe hepatic parenchymal damage as there may be changes in the absorption and biotransformation of trimethoprim and sulphamethoxazole.

Elderly patients

In elderly patients, a slight reduction in renal clearance of sulphamethoxazole but not trimethoprim has been observed.

Paediatric population

See special dosage regimen (see section 4.2).

5.3 Preclinical safety data

Reproductive toxicology: At doses in excess of recommended human therapeutic dose, trimethoprim and sulphamethoxazole 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

- Sucrose
- Sorbitol
- Sodium CMC
- Sodium benzoate
- Methyl paraben
- Citric acid
- Ethanol 96 %
- Tween 80
- Aerosil powder
- Tartrazine yellow
- Carmosine red
- Banana flavor

6.2 Incompatibilities

None known.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light. Keep in a well closed container. Keep out of reach of children.

6.5 Nature and contents of container

Pack size: 1 x 50ml.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.0 MANUFACTURER

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