

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

KRISHAT FRUSEMIDE (FRUSEMIDE TABLETS B.P. 40 MG)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Label claim

Each uncoated tablet contains:

Frusemide B.P.40mg

List of Excipients:

Colloidal anhydrous silica, Magnesium Stearate, Maize Starch, Dibasic calcium Phosphate, Cross carmellose sodium, Polyvinyl Pyrrolidone K-90, Methyl Paraben, Propyl Paraben, Sodium Starch Glycolate, Purified Talc & Sodium Benzoate

3. PHARMACEUTICAL FORM

Off white coloured, circular, flat, uncoated tablets with a break line on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Frusemide is a potent diuretic with rapid action. Frusemide tablets are indicated for:

- The treatment of fluid retention associated with heart failure, including left ventricular failure, cirrhosis of the liver and renal disease, including nephrotic syndrome.
- The treatment of mild to moderate hypertension when brisk diuretic response is required. Alone or in combination with other anti-hypertensive agents in the treatment of more severe cases.

4.2 Posology and method of administration

For oral administration.

Adults: The initial adult dose is 40mg daily, reduced to 20mg daily or 40mg on alternative days. In some patient's daily doses of 80mg or higher (given in divided doses) may be required.

Elderly: Caution is advised as frusemide is excreted more slowly in the elderly. Treatment should be started with 20mg and titrated upwards as required (see section 4.4).

Children: Contra-indicated (see section 4.3)

4.3 Contraindications

- Hypersensitivity to frusemide, amiloride, sulphonamides or sulphonamide derivatives, and/or any of the excipients of the product.
- Hypovolaemia and dehydration (with or without accompanying hypotension) (see section 4.4)
- Severe hypokalaemia: severe hyponatraemia (see section 4.4).
- Comatose or pre-comatose states associated with hepatic cirrhosis (see section 4.4).
- Anuria or renal failure with anuria not responding to frusemide, renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents or renal failure associated with hepatic coma
- Impaired renal function with a creatinine clearance below 30ml/min per 1.73 m² body surface area (see section 4.4).
- Addison's disease (see section 4.4).
- Children and adolescents under 18 years of age (safety in this age group has not yet been established).
- Digitalis intoxication (see section 4.5).
- Concomitant potassium supplements or potassium sparing diuretics (see section 4.5).
- Porphyria
- Breast-feeding women (see section 4.6).

4.4 Special warnings and precautions for use

Conditions requiring correction before frusemide is started (see also section 4.3)

- Hypotension.
- Hypovolaemia.
- Severe electrolyte disturbances – particularly hypokalaemia, hyponatraemia and acid-base disturbances.

Frusemide is not recommended

- In patients at high risk for radiocontrast nephropathy - it should not be used for diuresis as part of the preventative measures against radiocontrast-induced nephropathy.
- In patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Particular caution and/or dose reduction required:

- elderly patients (lower initial dose as particularly susceptible to side-effects - see section 4.2)
- difficulty with micturition including prostatic hypertrophy (increased risk of urinary retention: consider lower dose). Closely monitor patients with partial occlusion of the urinary tract
- diabetes mellitus (latent diabetes may become overt: insulin requirements in established diabetes may increase: stop frusemide before a glucose tolerance test)
- pregnancy (see section 4.6)

- gout (frusemide may raise uric acid levels/precipitate gout)
- patients with hepatorenal syndrome
- impaired hepatic function (see section 4.3 and below – monitoring required)
- impaired renal function (see section 4.3 and below – monitoring required)
- adrenal disease (see section 4.3 – contraindication in Addison's disease)
- hypoproteinaemia e.g. nephrotic syndrome (effect of frusemide may be impaired and its ototoxicity potentiated - cautious dose titration required).
- acute hypercalcaemia (dehydration results from vomiting and diuresis - correct before giving frusemide). Treatment of hypercalcaemia with a high dose of frusemide results in fluid and electrolyte depletion - meticulous fluid replacement and correction of electrolyte required.
- Patients who are at risk from a pronounced fall in blood pressure
- premature infants (possible development nephrocalcinosis/nephrolithiasis; renal function must be monitored and renal ultrasonography performed).
- Symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with frusemide, particularly in the elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension

Avoidance with other medicines (see also section 4.5 for other interactions)

- concurrent NSAIDs should be avoided – if not possible diuretic effect of frusemide may be attenuated
- ACE-inhibitors & Angiotensin II receptor antagonists – severe hypotension may occur – dose of frusemide should be reduced/stopped (3 days) before starting or increasing the dose of these

Laboratory monitoring requirements:

- Serum sodium

Particularly in the elderly or in patients liable to electrolyte deficiency

- Serum potassium

The possibility of hypokalaemia should be taken into account, in particular in patients with cirrhosis of the liver, those receiving concomitant treatment with corticosteroids, those with an unbalanced diet and those who abuse laxatives. Regular monitoring of the potassium, and if necessary treatment with a potassium supplement, is recommended in all cases, but is essential at higher doses and in patients with impaired renal function. It is especially important in the event of concomitant treatment with digoxin, as potassium deficiency can trigger or exacerbate the symptoms of digitalis intoxication (see section 4.5). A potassium-rich diet is recommended during long-term use.

Frequent checks of the serum potassium are necessary in patients with impaired renal function and creatinine clearance below 60ml/min per 1.73m² body surface area as well as in cases where frusemide is taken in combination with certain other drugs which may lead to an increase in

potassium levels (see section 4.5 & refer to section 4.8 for details of electrolyte and metabolic abnormalities)

- Renal function

Frequent BUN in first few months of treatment, periodically thereafter. Long-term/high-dose BUN should regularly be measured. Marked diuresis can cause reversible impairment of kidney function in patients with renal dysfunction. Adequate fluid intake is necessary in such patients. Serum creatinine and urea levels tend to rise during treatment

- Glucose

Adverse effect on carbohydrate metabolism - exacerbation of existing carbohydrate intolerance or diabetes mellitus. Regular monitoring of blood glucose levels is desirable.

- Other electrolytes

Patients with hepatic failure/alcoholic cirrhosis are particularly at risk of hypomagnesemia (as well as hypokalaemia). During long-term therapy (especially at high doses) magnesium, calcium, chloride, bicarbonate and uric acid should be regularly measured.

Clinical monitoring requirements (see also section 4.8):

Regular monitoring for

- blood dyscrasias. If these occur, stop frusemide immediately
- liver damage
- idiosyncratic reactions

Other alterations in lab values

- Serum cholesterol and triglycerides may rise but usually return to normal within 6 months of starting frusemide

Concomitant use with risperidone

In risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with frusemide plus risperidone (7.3%; mean age 89 years, range 75-97 years) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96 years) or frusemide alone (4.1%; mean age 80 years, range 67-90 years). Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be avoided in elderly patients with dementia (see section 4.3 Contraindications).

4.5 Interaction with other medicinal products and other forms of interaction

General- The dosage of concurrently administered cardiac glycosides, diuretics, anti-hypertensive agents, or other drugs with blood-pressure-lowering potential may require adjustment as a more pronounced fall in blood pressure must be anticipated if given concomitantly with frusemide.

The toxic effects of nephrotoxic drugs may be increased by concomitant administration of potent diuretics such as frusemide.

Some electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome).

Antihypertensives – enhanced hypotensive effect possible with all types. Concurrent use with ACE inhibitors or Angiotensin II receptor antagonists can result in marked falls in blood pressure, frusemide should be stopped or the dose reduced before starting an ACE-inhibitor or Angiotensin II receptor antagonists (see section 4.4)

Antipsychotics – frusemide -induced hypokalaemia increases the risk of cardiac toxicity. Avoid concurrent use with pimozide. Increased risk of ventricular arrhythmias with amisulpride or sertindole. Enhanced hypotensive effect with phenothiazines.

When administering risperidone, caution should be exercised and the risks and benefits of the combination or co-treatment with frusemide or with other potent diuretics should be considered prior to the decision to use. See section 4.4 Special warnings and precautions for use regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

Anti-arrhythmics (including amiodarone, disopyramide, flecainide and sotalol) - risk of cardiac toxicity (because of frusemide -induced hypokalaemia). The effects of lidocaine, tocainide or mexiletine may be antagonised by frusemide.

Cardiac glycosides – hypokalaemia and electrolyte disturbances (including hypomagnesia) increase the risk of cardiac toxicity.

Drugs that prolong Q-T interval – increased risk of toxicity with frusemide -induced electrolyte disturbances

Vasodilators – enhanced hypotensive effect with moxislyte (thymoxamine) or hydralazine

Other diuretics – profound diuresis possible when frusemide given with metolazone. Increased risk of hypokalaemia with thiazides. Contraindicated with potassium sparing diuretics (eg Amiloride spironolactone) - increased risk of hyperkalaemia (see section 4.3)

Renin inhibitors – aliskiren reduces plasma concentrations of frusemide

Nitrates – enhanced hypotensive effect

Lithium - In common with other diuretics, serum lithium levels may be increased when lithium is given concomitantly with frusemide, resulting in increased lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that lithium levels are

carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

Chelating agents – sucralfate may decrease the gastro-intestinal absorption of frusemide – the 2 drugs should be taken at least 2 hours apart

NSAIDs – increased risk of nephrotoxicity. Indometacin and ketorolac may antagonise the effects of frusemide (avoid if possible see section 4.4)

Salicylates – effects may be potentiated by frusemide. Salicylic toxicity may be increased by frusemide

Antibiotics – increased risk of ototoxicity with aminoglycosides, polymixins or vancomycin - only use concurrently if compelling reasons. Increased risk of nephrotoxicity with aminoglycosides or cefaloridine. Frusemide can decrease vancomycin serum levels after cardiac surgery. Increased risk of hyponatraemia with trimethoprim. Impairment of renal function may develop in patients receiving concurrent treatment with frusemide and high doses of certain cephalosporins.

Antidepressants – enhanced hypotensive effect with MAOIs. Increased risk of postural hypotension with TCAs (tricyclic antidepressants). Increased risk of hypokalaemia with reboxetine

Antidiabetics – hypoglycaemic effects antagonised by frusemide

Antiepileptics – increased risk of hyponatraemia with carbamazepine. Diuretic effect reduced by phenytoin.

Antihistamines – hypokalaemia with increased risk of cardiac toxicity

Antifungals – increased risk of hypokalaemia and nephrotoxicity with amphoterecin

Anxiolytics and hypnotics – enhanced hypotensive effect. Chloral or trichlorfos may displace thyroid hormone from binding site.

CNS stimulants (drugs used for ADHD) – hypokalaemia increases the risk of ventricular arrhythmias

Corticosteroids – diuretic effect antagonised (sodium retention) and increased risk of hypokalaemia

Glycyrrizin -(contained in liquorice) may increase the risk of developing hypokalaemia.

Carbenoxolone -may increase the risk of developing hypokalaemia

Cytotoxics – increased risk of nephrotoxicity and ototoxicity with platinum compounds/cisplatin. Nephrotoxicity of cisplatin may be enhanced if frusemide is not given in low doses (e.g. 40 mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Anti-metabolites – effects of frusemide may be reduced by methotrexate and frusemide may reduce renal clearance of methotrexate

Potassium salts – contraindicated - increased risk of hyperkalaemia (see section 4.3)

Dopaminergics – enhanced hypotensive effect with levodopa.

Immunomodulators – enhanced hypotensive effect with aldesleukin. Increased risk of hyperkalaemia with ciclosporin and tacrolimus. Increased risk of gouty arthritis with ciclosporin

Muscle relaxants – enhanced hypotensive effect with baclofen or tizanidine. Increased effect of curare-like muscle relaxants

Oestrogens – diuretic effect antagonised

Progestogens (drospiridone) – increased risk of hyperkalaemia

Prostaglandins – enhanced hypotensive effect with alprostadil

Sympathomimetics – increased risk of hypokalaemia with high doses of beta₂ sympathomimetics

Theophylline – enhanced hypotensive effect

Probenecid – effects of frusemide may be reduced by probenecid and frusemide may reduce renal clearance of probenecid.

Anaesthetic agents – general anaesthetic agents may enhance the hypotensive effects of frusemide.

The effects of curare may be enhanced by frusemide.

Alcohol – enhanced hypotensive effect

Laxative abuse - increases the risk of potassium loss

Others: Concomitant administration of aminoglutethimide may increase the risk of hyponatraemia.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is clinical evidence of safety of the drug in the third trimester of human pregnancy & frusemide has been given after the first trimester of pregnancy for oedema, hypertension and toxemia of pregnancy without causing fetal or newborn adverse effects. However, frusemide crosses the placental barrier and should not be given during pregnancy unless there are compelling medical reasons. It should only be used for the pathological causes of oedema which are not directly or indirectly linked to the pregnancy. The treatment with diuretics of oedema and hypertension caused by pregnancy is undesirable because placental perfusion can be reduced, so, if used, monitoring of fetal growth is required.

Lactation (see section 4.3)

Frusemide is contraindicated as it passes into breast milk and may inhibit lactation.

4.7 Effects on ability to drive and use machines

Reduced mental alertness, dizziness and blurred vision have been reported, particularly at the start of treatment, with dose changes and in combination with alcohol. Patients should be advised that if affected, they should not drive, operate machinery or take part in activities where these effects could put themselves or others at risk.

4.8 Undesirable effects

Undesirable effects can occur with the following frequencies: very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (> 1/10,000, < 1,000) and very rare (< 1/10,000, including isolated reports).

Blood and lymphatic system disorders:

Uncommon:

- thrombocytopenia

Rare:

- Eosinophilia
- Leukopenia
- Bone marrow depression (necessitates withdrawal of treatment). The haemopoietic status should be therefore be regularly monitored.

Very Rare:

- aplastic anaemia or haemolytic anaemia
- agranulocytosis

Nervous system disorders

Rare:

- paraesthesia
- hyperosmolar coma

Not known :

Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension)."

Endocrine disorder

Glucose tolerance may decrease with frusemide. In patients with diabetes mellitus this may lead to a deterioration of metabolic control; latent diabetes mellitus may become manifest. Insulin requirements of diabetic patients may increase.

Eye disorders

Uncommon: visual disturbance

Ear and labyrinth disorders

Hearing disorders and tinnitus, although usually transitory, may occur in rare cases, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephritic syndrome) and/or when intravenous frusemide has been given too rapidly.

Uncommon:

deafness (sometimes irreversible)"

Cardiac disorders

Uncommon: Cardiac arrhythmias

Frusemide may cause a reduction in blood pressure which, if pronounced may cause signs and symptoms such as impairment of concentration and reactions, light headedness, sensations of pressure in the head, headache, dizziness, drowsiness, weakness, disorders of vision, dry mouth, orthostatic intolerance.

Hepatobiliary disorders

In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis may develop.

Hepatic encephalopathy in patients with hepatocellular insufficiency may occur (see Section 4.3).

Vascular Disorder:

Rare:

- vasculitis

Skin and subcutaneous tissue disorders

Uncommon:

- Photosensitivity

Rare:

Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticaria, other rashes or bullous lesions, fever, hypersensitivity to light, exsudative erythema multiforme (Lyell's syndrome and Stevens-Johnson syndrome), bullous exanthema, exfoliative dermatitis, purpura, AGEP (acute generalized exanthematous pustulosis) and DRESS (Drug rash with eosinophilia and systemic symptoms).

Not Known:

Acute generalised exanthematous pustulosis (AGEP)

Metabolism and nutrition disorders

As with other diuretics, electrolytes and water balance may be disturbed as a result of diuresis after prolonged therapy. Frusemide leads to increased excretion of sodium and chloride and consequently increase excretion of water. In addition, excretion of other electrolytes (in particular potassium, calcium and magnesium) is increased.

Metabolic acidosis can also occur. The risk of this abnormality increases at higher dosages and is influenced by the underlying disorder (e.g. cirrhosis of the liver, heart failure), concomitant medication (see section 4.5) and diet.

Symptomatic electrolyte disturbances and metabolic alkalosis may develop in the form of a gradually increasing electrolyte deficit or e.g. where higher frusemide doses are administered to patients with normal renal function, acute severe electrolyte losses,

Symptoms of electrolyte imbalance depend on the type of disturbance:

Sodium deficiency can occur; this can manifest itself in the form of confusion, muscle cramps, muscle weakness, loss of appetite, dizziness, drowsiness and vomiting.

Potassium deficiency manifests itself in neuromuscular symptoms (muscular weakness, paralysis), intestinal symptoms (vomiting, constipation, meteorism), renal symptoms (polyuria) or cardiac symptoms. Severe potassium depletion can result in paralytic ileus or confusion, which can result in coma.

Magnesium and calcium deficiency result very rarely in tetany and heart rhythm disturbances.

Serum calcium levels may be reduced; in very rare cases tetany has been observed.

Nephrocalcinosis/Nephrolithiasis has been reported in premature infants.

Serum cholesterol (reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol) and triglyceride levels may rise during frusemide treatment. During long term therapy they will usually return to normal within six months,

As with other diuretics, treatment with frusemide may lead to transitory increase in blood creatinine and urea levels. Serum levels of uric acid may increase and attacks of gout may occur.

The diuretic action of frusemide may lead to or contribute to hypovolaemia and dehydration, especially in elderly patients. Severe fluid depletion may lead to haemoconcentration with a tendency for thromboses to develop.

General disorders and administration site conditions

Uncommon: Fatigue

Rare:

- Severe anaphylactic or anaphylactoid reactions (e.g. with shock) occur rarely.
- fever
- Malaise

Gastrointestinal disorders

Uncommon: dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhea, constipation. Gastro-intestinal disorders such as nausea, malaise or gastric upset (vomiting or diarrhoea) and constipation may occur but not usually severe enough to necessitate withdrawal of treatment.

Rare:

Acute Pancreatitis

Renal and urinary disorders

Uncommon:

- serum creatinine and urea levels can be temporarily elevated during treatment with frusemide.

Rare:

- interstitial nephritis, acute renal failure.

Increased urine production, urinary incontinence, can be caused or symptoms can be exacerbated in patients with urinary tract obstruction. Acute urine retention, possibly accompanied by complications, can occur for example in patients with bladder disorders, prostatic hyperplasia or narrowing of the urethra.

Pregnancy, puerperium and perinatal conditions

In premature infants with respiratory distress syndrome, administration of Frusemide Tablets in the initial weeks after birth entails an increased risk of a persistent patent ductus arteriosus.

In premature infants, frusemide can be precipitated as nephrocalcinosis/kidney stones.

Rare complications may include minor psychiatric disturbances.

4.9 Overdose

Features

Overdose can cause massive diuresis resulting in dehydration, volume depletion and electrolyte disturbances with consequent hypotension and cardiac toxicity. The clinical picture in acute or chronic overdose depends primarily on the extent and consequences of electrolyte and fluid loss, e.g. hypovolaemia, dehydration, haemoconcentration, cardiac arrhythmias due to excessive diuresis. Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion. High doses have the potential to cause transient deafness and may precipitate gout (disturbed uric acid secretion).

Management

- Benefits of gastric decontamination are uncertain. In patients presenting within 1 hour of ingestion, consider activated charcoal (50g for adults: 1g/kg for children)
- Observe for a minimum of 4 hours - monitor pulse and blood pressure.
- Treat hypotension and dehydration with appropriate IV fluids
- Monitor urinary output and serum electrolytes (including chloride and bicarbonate). Correct electrolyte imbalances. Monitor 12 lead ECG in patients with significant electrolyte disturbances

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: High-ceiling diuretic sulfonamides, loop diuretics;

ATC code: C03CA01

The evidence from many experimental studies suggests that frusemide acts along the entire nephron with the exception of the distal exchange site. The main effect is on the ascending limb of the loop of Henley with a complex effect on renal circulation. Blood-flow is diverted from the juxta-medullary region to the outer cortex.

The principle renal action of frusemide is to inhibit active chloride transport in the thick ascending limb. Re-absorption of sodium, chloride from the nephron is reduced hypotonic or isotonic urine produced.

It has been established that prostaglandin (PG) biosynthesis the renin-angiotensin system are affected by frusemide administration and that frusemide alters the renal permeability of the glomerulus to serum proteins.

5.2 Pharmacokinetic properties

Approximately 65% of the dose is absorbed after oral administration. The plasma half-life is biphasic with a terminal elimination phase of about 1½ hours. Frusemide is up to 99% bound to plasma proteins and is mainly excreted in the urine, largely unchanged, but also excreted in the bile, non-renal elimination being considerably increased in renal failure. Frusemide crosses the placental barrier and is excreted in the milk.

Frusemide is a weak carboxylic acid which exists mainly in the dissociated form in the gastrointestinal tract. Frusemide is rapidly but incompletely absorbed (60-70%) on oral administration and its effect is largely over within 4 hours. The optimal absorption site is the upper duodenum at pH 5.0. Regardless of route of administration 69-97% of activity from a radio-labelled dose is excreted in the first 4 hours after the drug is given. Frusemide is bound to plasma albumin and little biotransformation takes place. Frusemide is mainly eliminated via the kidneys (80-90%); a small fraction of the dose undergoes biliary elimination and 10-15% of the activity can be recovered from the faeces.

In renal/ hepatic impairment

Where liver disease is present, biliary elimination is reduced up to 50%. Renal impairment has little effect on the elimination rate of frusemide, but less than 20% residual renal function increases the elimination time.

The elderly

The elimination of frusemide is delayed in the elderly where a certain degree of renal impairment is present.

New born

A sustained diuretic effect is seen in the newborn, possibly due to immature tubular function.

5.3 Preclinical safety data

No further information available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica, Magnesium Stearate, Maize Starch, Dibasic calcium Phosphate, Cross carmellose sodium, Polyvinyl Pyrrolidone K-90, Methyl Paraben, Propyl Paraben, Sodium Starch Glycolate, Purified Talc & Sodium Benzoate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a cool, dark and dry place below 30°C & keep out of reach of children.

6.5 Nature and contents of container

25 X 10 Tablets in strip

6.6 Instructions for use and handling and disposal

No special requirements.

7. Marketing authorization holder

Krishat Pharma Industries Limited
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NIGERIA.
Email: info@krishatpharma.com