Registration for KENYA
HYOPLUS (Hyoscine Butyl bromide 10 Mg and Paracetamol 500 Mg Tablets)

---

1. Name of the medicinal product

HYOPLUS (Hyoscine Butyl bromide 10 Mg and Paracetamol 500 Mg Tablets)

2. Qualitative and quantitative composition

Each film coated tablet contains:
Hyoscine Butylbromide BP……10 mg
Paracetamol BP……...500 mg
Excipients……Q.S.
Colour: Titanium dioxide
(For the full list of excipients, see section 6.1)

3. Pharmaceutical form

Film coated tablet.
A white coloured, oblong shaped, film coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Hyoscine butylbromide and paracetamol belongs to a group of medicines called antispasmodic agents used to relieve abdominal pain/cramps. Abdominal pain occurs between the chest and pelvic region. The common causes of abdominal pain include inflammation, infections, intestinal disorders and obstruction/blockage. This medicine allows cramped muscles to relax simultaneously deliver fast relief from pain.

4.2 Posology and method of administration

The recommended dose for adults and adolescents over 12 years: 1-2 tablets three times daily
The maximum daily dose (24 hours) should not exceed 6 tablets.
Hyoplus should not be taken for longer than 3 days unless prescribed by a physician.

Method of administration

For oral use only.
The tablets should be swallowed whole with adequate liquid

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- myasthenia gravis
- mechanical narrowing (stenosis) in the gastrointestinal tract
- paralytic or obstructive ileus
- megacolon
- narrow angle glaucoma
- urinary retention due to mechanical narrowing of the urinary tract as in an enlarged prostate
- in rapid, racing, irregular heartbeat
- severe liver disease

4.4 Special warnings and precautions for use

Hyoscine Butylbromide

In case severe, unexplained abdominal pain persists or worsens, or occurs together with symptoms like fever, nausea, vomiting, changes in bowel movements, abdominal tenderness, decreased blood pressure, fainting, or blood in stool, medical advice should immediately be

sought.

Hyoplus Tablets should be used with caution in conditions characterized by tachycardia such as thyrotoxicosis, cardiac insufficiency or failure and in cardiac surgery where it may further accelerate the heart rate. Due to the risk of anticholinergic complications, caution should be used in patients susceptible to intestinal or urinary outlet obstructions.

Elevation of intraocular pressure may be produced by the administration of anticholinergic agents such as Hyoplus tablets in patients with undiagnosed and therefore untreated narrow angle glaucoma. Therefore, patients should seek urgent ophthalmological advice in case they should develop a painful, red eye with loss of vision whilst or after taking Hyoplus.

Paracetamol
Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

Do not exceed the recommended dose.

Do not take Hyoplus tablets for more than 3 days without consulting a doctor.

Do not take with any other paracetamol-containing products.

4.5 Interaction with other medicinal products and other forms of interaction

Hyoscine ButylBromide
The anticholinergic effect of drugs such as tri- and tetracyclic antidepressants, antihistamines, quinidine, amantadine, antipsychotics (e.g. butyrophenones, phenothiazines), disopyramide and other anticholinergics (e.g. tiotropium, ipratropium, atropine-like compounds) may be intensified by Hyoplus.
Concomitant treatment with dopamine antagonists such as metoclopramide may result in diminution of the effects of both drugs on the gastrointestinal tract.
The tachycardic effects of beta-adrenergic agents may be enhanced by Hyoplus.

Paracetamol
The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.
The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.
Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of hyoscine butylbromide in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. As a precautionary measure Hyoplus is not recommended during pregnancy.

Breast-feeding
There is insufficient information on the excretion of hyoscine butylbromide and its metabolites in human milk. A risk to the breastfeeding child cannot be excluded. Use of Hyoplus during breastfeeding is not recommended.

4.7 Effects on ability to drive and use machines
Paracetamol has no influence on the ability to drive and use machines. No studies on the effects on the ability to drive and use machines have been performed for hyoscine butylbromide. Because of possible visual accommodation disturbances patients should not drive or operate machinery if affected.

4.8 Undesirable effects
Many of the listed undesirable effects can be assigned to the anticholinergic properties of hyoscine butylbromide.
Adverse events have been ranked under headings of frequency using the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to <1/100); rare (≥ 1/10000 to <1/1000); very rare (<1/10000); not known (cannot be estimated from the available data).

Immune system disorders
Not known*: anaphylactic shock, anaphylactic reactions, dyspnoea, other hypersensitivity including skin rash may occur, angioedema

Blood and lymphatic system disorders
Not known: blood dyscrasias including thrombocytopenia and agranulocytosis

Cardiac disorders
Uncommon: tachycardia

Gastrointestinal disorders:
Uncommon: dry mouth

Skin and subcutaneous tissue disorders
Uncommon: skin reactions (e.g. urticaria, pruritus), abnormal sweating
Not known*: rash, erythema

Renal and urinary disorders
Rare: urinary retention

Metabolism and nutrition disorders
Not known: high anion gap metabolic acidosis.

Description of selected adverse reactions
High anion gap metabolic acidosis
Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol. Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is

important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org'.

4.9 Overdose

Hyoscine Butylbromide

Symptoms:

In the case of overdosage, anticholinergic effects such as urinary retention, dry mouth, reddening of the skin, tachycardia, inhibition of gastrointestinal motility and transient visual disturbances may occur, and Cheynes-Stokes respiration has been reported.

Therapy:

In the case of oral poisoning, gastric lavage with medicinal charcoal should be followed by magnesium sulfate (15%). Symptoms of overdosage respond to parasympathomimetics. For patients with glaucoma, pilocarpine should be given locally. Cardiovascular complications should be treated according to usual therapeutic principles. In case of respiratory paralysis, intubation and artificial respiration should be considered. Catheterisation may be required for urinary retention. In addition, appropriate supportive measures should be administered as required.

Paracetamol

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage if the patient has risk factors such as:
If the patient:

- is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. John's Wort or other drugs that induce liver enzymes, or
- regularly consumes ethanol in excess of recommended amounts, or
- is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia. Symptoms

Symptoms of paracetamol overdosage, in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, disseminated intravascular coagulation, haemorrhage, hypoglycaemia, cerebral oedema, gastrointestinal bleeding and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N- acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line

with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Further measures will depend on the severity, nature and course of clinical symptoms of paracetamol intoxication and should follow standard intensive care protocols.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Hyoscine butylbromide
ATC code: A03BB01

Hyoscine exerts a spasmolytic action on the smooth muscle of the gastrointestinal, biliary and genito-urinary tracts. As a quaternary ammonium derivative, hyoscine butylbromide does not enter the central nervous system. Therefore, anticholinergic side effects at the central nervous system do not occur. Peripheral anticholinergic action results from a ganglion-blocking action within the visceral wall as well as from an anti-muscarinic activity.

Paracetamol
ATC code: N02B E01, Other analgesics and antipyretics

Paracetamol is an effective analgesic and antipyretic agent, but has only weak anti-inflammatory properties. Its mechanism of action is not fully understood. It has been suggested that it may act predominantly by inhibiting prostaglandin synthesis in the CNS and to a lesser extent through a peripheral action by blocking pain-impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation. Paracetamol probably produces an antipyretic action by a central effect on the hypothalamic heat-regulating centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus. The drug has no effect on the cardiovascular and respiratory systems, and unlike salicylates it does not cause gastric irritation or bleeding.

5.2 Pharmacokinetic properties

Hyoscine butylbromide
Absorption
As a quaternary ammonium compound, hyoscine butylbromide is highly polar and hence only partially absorbed following oral (8%) or rectal (3%) administration. After oral administration of single doses of hyoscine butylbromide in the range of 20 to 400 mg, mean peak plasma concentrations between 0.11 ng/mL and 2.04 ng/mL were found at approximately 2 hours. In the same dose range, the observed mean $AUC_{0\text{-}tz}$-values varied from 0.37 to 10.7 ng h/mL. The median absolute bioavailabilities of different dosage forms, i.e. coated tablets, suppositories and oral solution, containing 100 mg of hyoscine butylbromide each were found to be less than 1%.

Distribution
Because of its high affinity for muscarinic receptors and nicotinic receptors, hyoscine butylbromide is mainly distributed on muscle cells of the abdominal and pelvic area as well as in the intramural ganglia of the abdominal organs. Plasma protein binding (albumin) of hyoscine butylbromide is approximately 4.4%. Animal studies demonstrate that hyoscine butylbromide does not pass the blood-brain barrier, but no clinical data to this effect is available. Hyoscine butylbromide (1 mM) has been observed to interact with the choline

transport (1.4 nM) in epithelial cells of human placenta *in vitro*.

Metabolism and elimination
Following oral administration of single doses in the range of 100 to 400 mg, the terminal elimination half-lives ranged from 6.2 to 10.6 hours. The main metabolic pathway is the hydrolytic cleavage of the ester bond. Orally administered hyoscine butylbromide is excreted in the faeces and in the urine. Studies in man show that 2 to 5% of radioactive doses is eliminated renally after oral, and 0.7 to 1.6% after rectal administration. Approximately 90% of recovered radioactivity can be found in the faeces after oral administration. The urinary excretion of hyoscine butylbromide is less than 0.1% of the dose. The mean apparent oral clearances after oral doses of 100 to 400 mg range from 881 to 1420 L/min, whereas the corresponding volumes of distribution for the same range vary from 6.13 to 11.3 x 10^5 L, probably due to very low systemic availability. The metabolites excreted via the renal route bind poorly to the muscarinic receptors and are therefore not considered to contribute to the effect of the hyoscine butylbromide.

Paracetamol
Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver (90-95%) and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.
A minor hydroxylated metabolite (N-acetyl-p-benzoquinoneimine) which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage. The time to peak plasma concentration of paracetamol is 0.5 to 2 hours, the time to peak effect 1 to 3 hours and the duration of action 3 to 4 hours.

5.3 Preclinical safety data
In limited reproductive toxicity studies hyoscine butylbromide showed no evidence of teratogenicity in rats at 200 mg/kg in the diet or in rabbits at 200 mg/kg by oral gavage or 50 mg/kg by subcutaneous injection. Fertility in the rat was not impaired at doses of up to 200 mg/kg in the diet.

6. Pharmaceutical particulars
6.1 List of excipients

- Microcrystalline Cellulose
- Colloidal Silicon Dioxide Light
- Starch
- Sodium Benzoate
- DM Water
- Talcum
- Magnesium Stearate
- Potassium Polacrilin
- Croscarmellose Sodium
- Hydroxypropyl Methyl Cellulose
- Polyethylene Glycol
- Methylene Dichloride
- Titanium Dioxide
- Isopropyl Alcohol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
1x10 Tablets in an Alu-PVC blister packed in carton

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder
Manufactured in India by:
RELAX BIOTECH PVT. LIMITED.
862/1, G.I.D.C, Makarpura,
Vadodara – 390 010, Gujarat, India.

Manufactured For & Marketed by:
KRISHNA CHEMISTS LTD.
P.O. BOX 3328-00506
Nairobi, Kenya.

8. Marketing authorisation number(s)

9. Date of first authorisation/renewal of the authorisation

10. Date of revision of the text
10/01/2025