For the use of Registered Medical Practitioner Only

1. Generic Name and Brand Name

Camylofin Dihydrochloride and Diclofenac Potassium Tablets
ANASPAS®

2. Qualitative and Quantitative composition

Each film coated tablet contains:

Camylofin Dihydrochloride	50mg
Diclofenac Potassium I.P.	50mg
Excipients	q.s.

Colours: Tartrazine Aluminum Lake, Brilliant Blue FCF Aluminum Lake, Ferrosoferric Oxide USP-NF Black, Titanium Dioxide I.P.

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

CARDIOVASCULAR THROMBOTIC EVENTS

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with the duration of use
- Diclofenac is contraindicated in the setting of coronary artery bypass graft (CABG) surgery

GASTROINTESTINAL BLEEDING, ULCERATION, AND PERFORATION

- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events

3. Dosage form and strength

Refer Section 1 & 2

4. Clinical Particulars

4.1. Therapeutic Indication

Indicated for short term management of abdominal colic pain.

4.2. Posology and method of administration

1 tablet every 12 hours after meals.

4.3. Contraindications

Camylofin is contraindicated in conditions such as Mega colon, GI haemorrhage, Tachyarrythmia, Porphyria, Glaucoma, Urinary retention (a dynamic bladder).

Diclofenac:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to diclofenac or any components of the drug product.

- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs.
- Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients.
- In the setting of coronary artery bypass graft (CABG) surgery

4.4 Special Warnings and precautions for use

Camylofin must be used with caution in

- elderly
- in patients with tachycardia and cardiac insufficiency
- paralytic ileus, ulcerative colitis and pylonic stenosis
- urinary retention and prostatic enlargement
- Pregnancy and in breast feeding.
- GERD as it may exacerbate it.

Diclofenac must be used with caution in
Gastrointestinal effects:
Gastrointestinal bleeding (haematemesis, melaena) ulceration or perforation which can be fatal has been reported with all NSAIDs including diclofenac and may occur at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

Hepatic effects:
Close medical surveillance is required when prescribing diclofenac to patients with impairment of hepatic function as their condition may be exacerbated.

Renal effects:
As fluid retention and oedema have been reported in association with NSAIDs therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery.

Skin effects:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis and generalised bullous fixed drug eruption have been reported very rarely in association with the use of NSAIDs.

Cardiovascular and cerebrovascular effects:
Patients with congestive heart failure (NYHA-I) or patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.

Pregnancy/Lactation
Category C

Children
Safety in children has not been established.

Worsening of hypertension and CV events, CCF and edema
NSAIDs such as diclofenac can lead to onset of new hypertension or worsening of pre-existing hypertension. This may lead to increased incidence of CV events.

Diclofenac potassium is a non-selective NSAID and is associated with an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. In patients with a risk of CV events, the lowest effective dose should be used for the shortest duration possible.

Congestive Heart Failure (CCF) and Edema may occur in some patients taking NSAIDs Serious gastrointestinal (GI) adverse events such as inflammation, and fatal complications such as bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal.

Patients and physicians should promptly initiate additional treatment if a serious GI adverse event is observed or suspected.

Renal Effects
Cautious use is recommended in patients with dehydration. Long term administration of NSAIDs can result in renal papillary necrosis and renal injury due to inhibition of prostaglandin synthesis and reduction in renal blood flow.

Patients at greatest risk of these reactions are elderly, those with renal or hepatic insufficiency, heart failure, patients those taking diuretics for recovery to the pre-treatment state.

In patients with renal disease close monitoring of the patient's renal function is advisable.

Hepatic Effects
Raised liver enzymes may occur during therapy with diclofenac potassium treated patients. Monitoring of the markers of hepatic function, ALT (SGPT) is recommended.

Cases of drug-induced hepatotoxicity have been reported in the first or second month of treatment but can occur at any time during treatment with diclofenac. Severe hepatic reactions reported include liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and post marketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating

treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac.

If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop ANASPAS should be discontinued immediately. Physicians should educate patients of the warning signs and symptoms indicative of hepatotoxicity such as pruritus, nausea, fatigue, lethargy, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms, and must initiate the appropriate action patients should take if these signs and symptoms appear.

Caution must be exercised when prescribing ANASPAS with concomitant drugs that are may be potentially hepatotoxic such as antibiotics, anti-epileptic drugs.

Skin Reactions
NSAIDs, including such as diclofenac potassium can cause serious fatal skin adverse events such as exfoliative dermatitis, Stevens - Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).

Special patient populations
Pediatric: Diclofenac pharmacokinetic have not been studied in pediatric patients.

Hepatic Insufficiency: In hepatic insufficiency, reduction of dose of diclofenac is required since it is metabolised almost 100% in the liver

Renal Insufficiency: Diclofenac pharmacokinetics is not altered in patients with renal impairment.

Pregnancy
In late pregnancy, diclofenac potassium must be avoided because it may cause premature closure of the ductus arteriosus, as has been observed with any other NSAIDs.

4.5 Drug-Drug interactions

The important drug interactions are listed below:
Camylofin

- Antacids interfere with absorption of camylofin.
- Antihistaminic, tricyclic antidepressants, phenothiazines, disopyramide, pethidine have anticholinergic property-additive effects occur with Camylofin.

Diclofenac drug interactions

Drug	Effect
Voriconazole	The Cmax and AUC of diclofenac increased by 114% and 78%, respectively

Lithium	If used concomitantly, diclofenac may increase plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.
Digoxin	If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.
Diuretics and antihypertensive agents	Like other NSAIDs, concomitant use of diclofenac with diuretics and antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.
Anticoagulants and anti-platelet agents	Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac has an influence on the effect of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulant concomitantly
Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids	Co administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs.
Methotrexate	Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increase.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

There is no data on the safety and efficacy of camylofin in pregnant women. Hence, it is not recommended for use in pregnancy.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and or cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1% up to approximately 1.5%.

The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has shown to result in increased pre- and post-implantation loss and embryo-foetal lethality.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during organogenetic period.
From the 20th week of pregnancy onward, Diclofenac Potassium use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arterious constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore**,** during the first and second trimester of pregnancy, Diclofenac Potassium should not be given unless clearly necessary.
If Diclofenac Potassium is used by a woman attempting to conceive, or during the first or second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to diclofenac for several days from gestational week 20 onward. Diclofenac Potassium should be discontinued if oligohydramnios or ductus arteriosus constriction is found.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);
the mother and the neonate, at the end of the pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.
Consequently, Diclofenac Potassium is contraindicated during the third trimester of pregnancy.

In late pregnancy, diclofenac potassium must be avoided because it may cause premature closure of the ductus arteriosus as has been observed with any other NSAIDs.

Lactation
There is no data on the safety and efficacy of Camylofin (tablet) in lactating women. Hence, it is not recommended for use in lactating mother. Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, diclofenac should not be administered during breast-feeding in order to avoid adverse effects in the infant.

Pediatric
There is no specific contraindication for use of Camylofin in children.
For children over 14 years of age, the recommended daily dose is 75-100 mg in two or three divided doses. Diclofenac Potasssium tablets are not recommended for children under 14 years of age.

Geriatric
Camylofin should be used with caution in elderly.

Caution is indicated in the elderly when diclofenac is prescribed.
Although the pharmacokinetics of diclofenac sodium are not impaired to any clinically relevant extent in elderly patients, nonsteroidal anti-inflammatory drugs should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight (see also precautions) and the patient should be monitored for GI bleeding during NSAID therapy.
There are no significant overall differences in safety or effectiveness between elderly subjects and younger subjects.

4.7 Effects on ability to drive and use machines
Patients who experience visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances, drowsiness, or fatigue while taking NSAIDs should refrain from driving or operating machinery.

4.8 Undesirable effects
Anticholinergic adverse reactions may occur with camylofin such as transient tachycardia, Dry mouth, Redness, Disturbances of accommodation, reduced sweating. Other side effects reported include glaucoma, nausea, and drowsiness.

Diclofenac:
Adverse reactions are ranked under the heading of frequency, the most frequent first, using the following convention: very common: (>1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000); not known: cannot be estimated from available data.
The following undesirable effects include those reported with other short-term or long-term use.

Table 1

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leucopoenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.
Immune system disorders	
Rare Very rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock). Angioneurotic oedema (including face oedema).
Psychiatric disorders	

Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common Rare Very rare Unknown	Headache, dizziness. Somnolence, tiredness. Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident. Confusion, hallucinations, disturbances of sensation, malaise.
Eye disorders	
Very rare Unknown	Visual disturbance, vision blurred diplopia. Optic neuritis.
Ear and labyrinth disorders	
Common Very rare	Vertigo. Tinnitus, hearing impaired.
Cardiac disorders	
Uncommon*	Myocardial infarction, cardiac failure, palpitations, chest pain.
Not known	Kounis syndrome.
Vascular disorders	
Very rare	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare Very rare	Asthma (including dyspnoea). Pneumonitis.
Gastrointestinal disorders	
Common Rare Very rare	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.

Unknown	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly). Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis. Ischaemic colitis.
Hepatobiliary disorders	
Common Rare Very rare	Transaminases increased. Hepatitis, jaundice, liver disorder. Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common Rare Very rare Not Known	Rash. Urticaria. Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus. Fixed drug eruption, generalised bullous fixed drug eruption.
Renal and urinary disorders	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
Reproductive system and breast disorders	
Very rare	Impotence.
General disorders and administration site conditions	
Rare	Oedema.

** The frequency reflects data from long-term treatment with a high dose (150 mg/day).*

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high doses (150mg daily) and in long term treatment (see sections 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use).

4.9 Overdose

ANASPAS has diclofenac potassium which is a NSAID. Symptoms observed after acute NSAID overdoses include lethargy, drowsiness, nausea, vomiting, and epigastric pain. These can be corrected / reversed with supportive care.

Gastrointestinal bleeding may be observed. Additionally, hypertension, acute renal failure, respiratory depression, Anaphylactoid reactions and coma may occur rarely but are rare.

Symptomatic and supportive care is recommended for management of NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be administered in patients brought to medical attention within 4 hours of ingestion with symptoms or after a large overdose (5 to 10 times the usual dose). The high protein binding of diclofenac makes forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion ineffective for the management of overdose.

5 Pharmacological properties

5.1 Mechanism of action

Camylofin is a spasmolytic agent with a potent dual mode of action, i.e. it possesses both musculotropic and neurotropic effects.

Camylofin has a direct papaverine like spasmolytic action on smooth muscles, where it inhibits the enzyme phosphodiesterase IV, which in turn causes an increase in intracellular concentration of cyclic AMP and smooth muscle relaxation by depletion of intracellular calcium levels. This is the more predominant action of camylofin.

Camylofin also possesses a neurotropic action i.e. a mild atropine like anti-cholinergic effect, where by it causes smooth muscle relaxation, by inhibiting the binding of acetylcholine with the muscarinic receptors.

Diclofenac is a potent inhibitor of prostaglandin biosynthesis and a modulator of arachidonic acid release and uptake.

5.2 Pharmacodynamic properties

Camylofin is a smooth muscle relaxant. It has both anticholinergic actions and direct smooth muscle relaxant actions. Anticholinergic effects are seen due to inhibition of the binding of acetylcholine to muscarinic receptors. Direct smooth muscle relaxation is due to the inhibition of phosphodiesterase type IV, which results in increased cyclic AMP and subsequently reduced cytosolic calcium. Thus camylofin relieves smooth muscle spasms effectively due to the dual actions.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) that has anti-inflammatory, analgesic, and antipyretic activities. It inhibits the cyclooxygenase enzyme and inhibits the production of inflammatory mediators such as prostaglandins.

5.3 Pharmacokinetic properties

Camylofin is an anticholinergic antispasmodic with rapid pharmacokinetics, exhibiting a mean elimination half-life of approximately 1.16-1.68 hours. It shows high volume of distribution and high clearance, with maximum plasma concentration reached quickly (approx. 2.26-2.43ng/mL). Food intake can increase its half-life and alter clearance.

Camylofin is rapidly distributed in the body to various tissues. Most of the tissues (highest in liver), with the exception of the gastrointestinal tract (least), possess an esterase enzyme which cleaves camylofin into two pharmacologically weak metabolites (isoamylalcohol and alpha -N-(beta -diethyl aminoethyl)D-amino- phenylacetic acid. Camylofin is rapidly metabolized and only a small amount of it is excreted into the urine.

Almost 100% of diclofenac is absorbed after oral administration but due to first-pass metabolism, only about 50% of the absorbed dose is systemically available.

Food does not interfere with the absorption of diclofenac. But there may be a delay in onset of absorption and reduction in Cmax by 30%. Peak plasma levels (C max) occur in 1 hour in fasting volunteers. The Apparent volume of Distribution of diclofenac is 1.3 L/kg.

Five diclofenac metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy-diclofenac. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation and then biliary excretion. Acyl glucuronidation mediated by UGT2B7 and oxidation mediated by CPY2C8 may also help in the diclofenac metabolism. CYP3A4 causes the formation of minor metabolites, 5-hydroxy- and 3'-hydroxy-diclofenac.

More than 99% bound to human serum proteins, primarily to albumin. The half-life is 2 hours.

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

The dual mode of action of camylofin has been demonstrated in animal experiments, where in camylofin abolished the spasm-inducing effects of both carbachol (cholinergic spasms) and barium chloride (muscular spasms.)

In mini pigs, diclofenac sodium dose-related clinical signs and alterations of hematological or clinical chemistry parameters, organ weight, and macroscopic as well as histopathological findings in hepatic, renal, gastrointestinal, skin and injection sites were observed in both sexes' animals of the 10 or 20 mg/kg/day group.

7 Description

Light green to green colored film coated, round shaped tablets, plain on both sides.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not Applicable

8.2 Shelf-life

Refer pack

8.3 Packaging information

Refer pack

8.4 Storage and handling instructions

Store at a temperature not exceeding 25 °C, protected from light & moisture.

9 Patient Counselling Information

Patients must inform the doctor if they are allergic to Camylofin or Diclofenac or any other ingredient in Tab. Anaspas.

Patients should be advised that they must avoid taking this medicine if they have narrow-angle glaucoma (optic nerve damage due to sudden high eye pressure), prostatic hypertrophy (enlargement of prostate gland causing difficulty with urination) or urinary retention or constipation, heart problems.

Patients should be advised that they must inform their doctor if they have tachycardia, ulcerative colitis and gastroesophageal reflux disease or peptic ulcer disease.

Patients must be advised to take Anaspas in the dose prescribed by the doctor.

Patients must be advised to avoid taking NSAIDs like Diclofenac:

- if they have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, patients must tell doctor about all of their medical conditions, including if they:

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant.
- are breastfeeding or plan to breast feed.

Patients must not take NSAIDs after 29 weeks of pregnancy.

Patients must be advised to tell their doctor about all of the medicines they take, including prescription or over-the-counter medicines, vitamins, or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. Patients must not start taking any new medicine without talking to the doctor first.

10 Details of manufacturer

Manufactured by:

Abbott Healthcare Pvt. Ltd.
At: Plot No. 21-23, Industrial Area,
Phase I, Mehatpur, Distt. Una,
Himachal Pradesh – 174 315.

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