Vadis® Diclofenac Sodium (Gastro-resistant Diclofenac Tablets BP 50 mg)

Module 1- Administrative information and prescribing information

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

Summary Product Characteristics (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Vadis® Diclofenac Sodium
(Gastro-resistant Diclofenac Tablets BP 50 mg)

Strength

Each Enteric coated tablet contains:
Diclofenac sodium BP 50 mg
Excipients q.s.
Colour: Sunset Yellow FCF

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Description: Orange colored, round shaped, biconvex, Enteric coated tablets having both sides plain.

Sr. No.	Name of raw material	Spec	Label Claim (mg)	Qty/tab (mg)	Purpose of use
Dry Mixing					
1.	Diclofenac sodium*	BP	50.000	50.000	Active
2.	Maize Starch#	BP	-	30.00	Diluent
3.	Di Basic Calcium Phosphate	BP	-	28.00	Diluent
Binding					
4.	Maize Starch	BP	-	16.00	Binder
5.	Povidone (PVPK-30)	BP	-	9.00	Binder
6.	Purified water**	BP	-	61.22	Solvent
Pre-Lubrication					
7.	Sodium Starch glycolate	BP	-	15.20	Disintegrant
8.	Talcum	BP	-	5.60	Glidant
9.	Colloidal silicon dioxide	BP	-	1.50	Binder
10.	Sodium Lauryl Sulphate	BP	-	1.00	Lubricant
Lubrication					
11.	Magnesium Stearate	BP	-	3.90	Lubricant
Coating					
12.	Colour Ready Mix Enteric coat Sunset yellow FCF	In-House	-	30.00	Colouring agent

Sr. No.	Name of raw material	Spec	Label Claim (mg)	Qty/tab (mg)	Purpose of use
13.	Isopropyl alcohol**	BP	-	300.00	Solvent
14.	Methylene Dichloride**	BP		300.00	Solvent

BP: British Pharmacopeia

#Quantity to be compensates for Loss of Drying.
** Quantity evaporated during drying.

3. PHARMACEUTICAL FORM

Orange colored, round shaped, biconvex, Enteric coated tablets having both sides plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vadis® Diclofenac Sodium is indicated for patients who require the non-steroidal anti-inflammatory drug diclofenac together with misoprostol.
The diclofenac component of Vadis® Diclofenac Sodium is indicated for the symptomatic treatment of osteoarthritis and rheumatoid arthritis. The misoprostol component of Vadis® Diclofenac Sodium is indicated for patients with a special need for the prophylaxis of NSAID-induced gastric and duodenal ulceration.

4.2 Posology and method of administration

Posology
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.
Adults
One tablet to be taken with food, two or three times daily. Tablets should be swallowed whole, not chewed.
Elderly/renal, cardiac and hepatic impairment
No adjustment of dosage is necessary in the elderly or in patients with hepatic impairment or mild to moderate renal impairment as pharmacokinetics are not altered to any clinically relevant extent. Nevertheless, elderly patients and patients with renal, cardiac or hepatic impairment should be closely monitored.
Paediatric population
The safety and efficacy of Vadis® Diclofenac Sodium in children under 18 years has not been established.

4.3 Contraindications

Vadis® Diclofenac Sodium is contraindicated in:

- Patients with active peptic ulcer/haemorrhage or perforation or who have active GI bleeding or other active bleedings e.g., cerebrovascular bleedings.
- Pregnant women and in women planning a pregnancy.
- Women of childbearing potential who are not using effective contraception.
- Patients with a known hypersensitivity to diclofenac, acetylsalicylic acid, other NSAIDs, misoprostol, other prostaglandins, or any other ingredient of the product.
- Patients in whom, attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid or other non-steroidal anti-inflammatory agents.
- Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
- Patients with severe renal and hepatic failure.
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

Warnings

The use of diclofenac/misoprostol with concomitant systemic NSAIDs including COX-2 inhibitors should be avoided, except for patients requiring low dose acetylsalicylic acid – caution is advised in such patients with close monitoring. Concomitant use of a systemic NSAID and another systemic NSAID may increase frequency of gastrointestinal ulcers and bleeding.

- In women of childbearing potential

Vadis® Diclofenac Sodium must not be used unless they use effective contraception and have been advised of the risks of taking the product if pregnant.

The label will state: 'Not for use in women of childbearing potential unless using effective contraception'.

Precautions

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

- Renal/cardiac/hepatic impairment

In patients with renal, cardiac or hepatic impairment and in the elderly, caution is required since the use of NSAIDs may result in deterioration of renal function. In the following conditions Vadis® Diclofenac Sodium should be used only in exceptional circumstances and with close clinical monitoring: advanced liver disease, severe dehydration.

In a large trial where patients received diclofenac for a mean of 18 months, ALT/AST elevations were observed in 3.1% of patients. ALT/AST elevations usually occur within 1-6 months. In clinical trials, hepatitis has been observed in patients who received diclofenac, and in postmarketing experience, other hepatic reactions have been reported, including jaundice and hepatic failure. During diclofenac/misoprostol therapy, liver function should be monitored periodically. If diclofenac/misoprostol is used in the presence of impaired liver function, close

monitoring is necessary. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur treatment with diclofenac should be discontinued.

Diclofenac metabolites are eliminated primarily by the kidneys. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. As with other NSAIDs, metabolites of which are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.

In rare cases, NSAIDs, including diclofenac/misoprostol, may cause interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome. NSAIDs inhibit the synthesis of renal prostaglandin which plays a supportive role in the maintenance of renal perfusion in patients whose renal blood flow and blood volume are decreased. In these patients, administration of an NSAID may precipitate overt renal decompensation, which is typically followed by recovery to pretreatment state upon discontinuation of NSAID therapy. Patients at greatest risk of such a reaction are those with congestive heart failure, liver cirrhosis, nephrotic syndrome overt renal disease, and the elderly. Such patients should be carefully monitored while receiving NSAID therapy.

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

As with all NSAIDS, diclofenac/misoprostol can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. NSAIDs, including diclofenac/misoprostol, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with diclofenac/misoprostol and throughout the course of therapy.

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high dose (150 mg daily) and in long term treatment may be associated with a small increased risk of serious arterial thrombotic events (for example myocardial infarction or stroke).

Physicians and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur.

- Blood system/gastrointestinal

NSAIDs, including diclofenac/misoprostol, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. When GI bleeding or ulceration occurs in

patients receiving diclofenac/misoprostol, the treatment should be withdrawn. These events can occur at any time during treatment, with or without warning symptoms or in patients with a previous history of serious GI events.

Patients most at risk of developing these types of GI complications with NSAIDs are those treated at higher doses, the elderly, patients with cardiovascular disease, patients using concomitant acetylsalicylic acid, corticosteroids, selective serotonin reuptake inhibitors, patients who consume alcohol or patients with a prior history of, or active, gastrointestinal disease, such as ulceration, GI bleeding or inflammatory conditions. Therefore, diclofenac/misoprostol should be used with caution in these patients and commence on treatment at the lowest dose available.

NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution should be advised in patients receiving concomitant medicines which could increase the risk of ulceration or bleeding, such as oral corticosteroids, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin . The concomitant use of NSAIDs, including Vadis® Diclofenac Sodium, with oral anticoagulants increases the risk of GI and non-GI bleeding and should be given with caution. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, rivaroxaban). Anticoagulation/INR should be monitored in patients taking a warfarin/coumarin-type anticoagulant.

Vadis® Diclofenac Sodium in common with other NSAIDs, may decrease platelet aggregation and prolong bleeding time. Extra supervision is recommended in haematopoietic disorders or in conditions with defective coagulation or in patients with a history of cerebrovascular bleeding.

Caution is required in patients suffering from ulcerative colitis or Crohn's Disease as these conditions may be exacerbated.

Care should be taken in elderly patients and in patients treated with corticosteroids, other NSAIDs, or anti-coagulants.

- Skin reactions

Serious skin reactions, some of them fatal, including drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including diclofenac/misoprostol (see section 4.8). Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occurring in the majority of cases within the first month of treatment. Diclofenac/misoprostol should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

- Hypersensitivity

NSAIDs may precipitate bronchospasm in patients suffering from, or with a history of bronchial asthma or allergic disease.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac.

- Long-term treatment

All patients who are receiving long-term treatment with NSAIDs should be monitored as a precautionary measure (e.g. renal, hepatic function and blood counts). During long-term, high dose treatment with analgesic/anti-inflammatory drugs, headaches can occur which must not be treated with higher doses of the medicinal product.

- Vadis® Diclofenac Sodium may mask fever and thus an underlying infection.
- Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium content

Vadis® Diclofenac Sodium contains less than 1 mmol sodium (23 mg) per tablet. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

Hydrogenated castor oil

Vadis® Diclofenac Sodium also contains hydrogenated castor oil, which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with Vadis® Diclofenac Sodium gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.

Observed Interactions to be considered

CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac

CYP2C9 inducers: Caution is recommended when co-prescribing diclofenac with CYP2C9 inducers (such as rifampicin), which could result in a significant decrease in plasma concentration and exposure to diclofenac

Lithium: If used concomitantly, diclofenac may raise 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 or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme

(ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

Ciclosporin: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently.

Quinolone antibacterials: There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

Anticipated Interactions to be considered

Other NSAIDs and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal ulceration or Bleeding .

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 affects the action of anticoagulants, NSAIDs may enhance the effects of anti-coagulants, such as warfarin. There are also reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs including diclofenac and SSRIs may increase the risk of gastrointestinal bleeding.

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

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 or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

4.6 Fertility, pregnancy and lactation

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 of 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 been 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 the organogenetic period.

From the 20th week of pregnancy onward, diclofenac 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 arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, diclofenac should not be given unless clearly necessary. If diclofenac is used by a woman attempting to conceive, or during the first and 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 should be discontinued if oligohydramnios or ductus arteriosus constriction are 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 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 is contraindicated during the third trimester of pregnancy.

Lactation

Like other NSAIDs, diclofenac passes into the breast milk, but in small amounts. Therefore, Vadis® Diclofenac Sodium should not be administered during breast feeding in order to avoid undesirable effects in the infant.

Fertility

As with other NSAIDs, the use of Vadis® Diclofenac Sodium may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Vadis® Diclofenac Sodium should be considered.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo, somnolence or other central nervous system disturbances, including visual disturbances, while taking NSAIDs should refrain from driving or using machines.

4.8 Undesirable effects

Adverse drug reactions from clinical trials and/or spontaneous or literature cases are listed by MedRA system order class. Within each system organ class, the adverse drug reactions are ranked of frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (>1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000).

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur . Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of coilitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed.

The following table of undesirable effects include those reported with Vadis® Diclofenac Sodium gastro-resistant tablets and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Blood and lymphatic system disorders

Very rare: Thrombocytopenia, leucopenia, anemia (including haemolytic anemia and aplastic anaemia), agranulocytosis.

Immune system disorder

Rare: Hypersensitivity reactions such as asthma, systemic anaphylactic and anaphylactoid reactions (including hypotension and shock).

Very rare: Angioedema (including face oedema).

Psychiatric disorders

Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder

Nervous system disorders
Common: Headache, dizziness,
Rare: Somnolence,
Very rare: Paresthesia, memory impairment, convulsions, anxiety, tremor, meningitis asptic, dysgeusia, cerebrovascular accident.
Eye disorders
Very rare: Visual impairment (blurred vision, diplopia).
Ear and labyrinth disorders
Common: Vertigo.
Very rare: Tinnitus, hearing impaired.
Cardiac disorders
Uncommon*:
Frequency not known
Myocardial infarction, cardiac failure, palpitations, chest pain
Kounis syndrome
Vascular disorders
Very rare: Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders
Rare: Asthma/bronchospasm (including dyspnoea).
Very rare: Pneumonitis.
Gastrointestinal tract disorders
Common: Nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, decreased appetite.
Rare: Gastritis, gastrointestinal hemorrhage, hematemesis, melena, diarrhea hemorrhagic, gastric or intestinal ulcer (with or without bleeding or perforation).
Very rare:
Colitis (including hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis
Not known: Ischemic Colitis
Hepatobiliary disorders
Common: Transaminases increased.
Rare: Hepatitis, with or without jaundice, liver disorder.
Very rare: Hepatitis fulminant, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders

Common: Rashes.
Rare: Urticaria.
Very rare: Dermatitis bullous, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal, necrolysis (Lyell's syndrome) dermatitis exfoliative,alopecia, photosensitivity reaction, purpura, including allergic purpura, Henoch-Schonlein prpura, pruritus.

Renal and urinary disorders

Very rare: Acute kidney injury (acute renal failure), hematuria, proteinuria, nephritic syndrome, tubulointerstitial nephritis, renal papillary necrosis.

General disorders and administration site conditions

Rare: Edema

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic measures

Management of acute poisoning with NSAIDs, including diclofenac, consists essentially of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis, or haemoper fusion are probably unlikely to be helpful in accelerating the elimination of NSAIDs, including diclofenac, because of their high protein binding rate and extensive metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life threatening overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: non-steroidal anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances (NSAID) (ATC code: M01A B05).

Mechanism of action

Vadis® Diclofenac Sodium contains diclofenac sodium, a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic, and antipyretic properties. Inhibition of

prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action. Prostaglandins play a major role in causing of inflammation, pain, and fever.

Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to those reached in humans.

Pharmacodynamic effects

In rheumatic diseases, the anti-inflammatory and analgesic properties of Vadis® Diclofenac Sodium elicit a clinical response characterised by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function.

In post-traumatic and post-operative inflammatory conditions, Vadis® Diclofenac Sodium rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema.

In clinical trials Vadis® Diclofenac Sodium has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin. Clinical studies have also revealed that, in primary dysmenorrhoea, Vadis® Diclofenac Sodium is capable of relieving the pain and reducing the extent of bleeding.

There is limited clinical trial experience of the use of diclofenac in Juvenile Rheumatoid Arthritis (JRA)/Juvenile Idiopathic Arthritis (JIA) paediatric patients. In a randomized, doubleblind, 2-week, parallel group study in children aged 3-15 years with JRA/JIA, the efficacy and safety of daily 2-3 mg/kg BW diclofenac was compared with acetylsalicylic acid (ASS, 50-100 mg/kg BW/d) and placebo – 15 patients in each group. In the global evaluation, 11 of 15 diclofenac patients, 6 of 12 aspirin and 4 of 15 placebo patients showed improvement with the difference being statistically significant ($p < 0.05$). The number of tender joints decreased with diclofenac and ASS but increased with placebo. In a second randomized, double-blind, 6-week, parallel group study in children aged 4-15 years with JRA/JIA, the efficacy of diclofenac (daily dose 2-3 mg/kg BW, n=22) was comparable with that of indomethacin (daily dose 2-3mg/kg BW, n=23).

5.2 Pharmacokinetic properties

Absorption:

Diclofenac is completely absorbed from the gastro-resistant tablets after their passage through the stomach. Although absorption is rapid, its onset may be delayed due to the gastro-resistant coating of the tablet.

Mean peak plasma concentrations of 1.5 micrograms/mL (5 micromol/L) are attained on average 2 hours after ingestion of one tablet of 50 mg.

The passage of a tablet through the stomach is slower when ingested with or after a meal than when it is taken before a meal, but the amount of diclofenac absorbed remains the same.

Since about half of diclofenac is metabolized during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) following oral or rectal administration is about half that following an equivalent parenteral dose.

The amount absorbed is linearly related to the size of the dose.
The plasma concentrations attained in children given equivalent doses (mg/kg body weight) are similar to those obtained in adults.
Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

Distribution:

The active substance is 99.7% protein bound, mainly to albumin (99.4%).
Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after the peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3-6 hours. Two hours after reaching the peak plasma values, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma, and remain higher for up to 12 hours.
Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.

Biotransformation:

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination:

Total systemic clearance of diclofenac in plasma is 263±56ml/min (mean value ±SD). The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours.
About 60% of the administered dose is excreted in the urine as the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Special Populations

Elderly: No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed, other than the finding that in five elderly patients, a 15-minute iv infusion resulted in 50% higher plasma concentrations than expected with young healthy subjects.

Patients with renal impairment: In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of <10ml/min, the calculated steady-state plasma levels of hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

Patients with hepatic disease: In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

5.3 Preclinical safety data

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. In standard preclinical animal studies, there was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.

Diclofenac had no influence on the fertility of the parent animals (in rats). Except for minimal fetal effects at maternally toxic doses the prenatal, perinatal, and postnatal development of the offspring was not affected.

Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the ductus arteriosus in the pregnant rat. Maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation in rats. The slight effects of diclofenac on reproduction parameters and delivery as well as constriction of the ductus arteriosus in utero are pharmacologic consequences of this class of prostaglandin synthesis inhibitors.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Maize Starch	BP
Di Basic Calcium Phosphate	BP
Maize Starch	BP
Povidone (PVPK-30)	BP
Purified water	BP
Sodium Starch glycolate	BP
Talcum	BP
Colloidal silicon dioxide	BP
Sodium Lauryl Sulphate	BP
Magnesium Stearate	BP
Colour Ready Mix Enteric coat Sunset yellow FCF	In-house
Isopropyl alcohol	BP
Methylene Dichloride	BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30˚C. Protect from light.

6.5 Nature and contents of container

1 X 10 Alu-PVC Blister Pack

6.6 Special precautions for disposal and other handling

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. APPLICANT/MANUFACTURER

MANUFACTURED
First Vadis Pharmaceutical Industries Limited
Plot IN/2 Phase 2 Extension, Emene
Industrial Layout Enugu State