VADIS PHARMACEUTICALS LIMITED	
BRAND NAME:	**VADIS DICLOFENAC PLUS CAPSULES**
GENERIC NAME:	**PARACETAMOL AND DICLOFENAC CAPSULES BP 525 MG**

MODULE 1 – ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product
Vadis Diclofenac Plus Capsules (Paracetamol and Diclofenac Capsules 525 mg)

2. Qualitative and quantitative composition
Each capsule contains
Paracetamol BP 500 mg
Diclofenac Sodium BP 25 mg

3. Pharmaceutical form
Hard Capsules.
Pink coloured capsule

4. Clinical particulars

4.1 Therapeutic indications
Paracetamol has analgesic and antipyretic actions similar to those of aspirin and hence is a suitable alternative for patients sensitive to aspirin. For the relief of mild to moderate pain and febrile conditions, *eg* headache, toothache, colds, influenza, rheumatic pain and dysmenorrhoea.
Low back pain, Migraine attacks, Acute musculo-skeletal disorders and trauma such as periarthritis (especially frozen shoulder), tendinitis, tenosynovitis, bursitis, sprains, strains and dislocations; relief of pain in fractures

4.2 Posology and method of administration
Adults including the elderly and children over 16 years: One to two tablets every 4-6 hours as required, to a maximum of 8 tablets daily in divided doses.
Children 10-15 years: One tablet every 4-6 hours as necessary to a maximum of 4 doses in 24 hours.
Children under 10 years: Not recommended for children under 10 years of age. Alternative presentations of paracetamol are recommended for paediatric usage in order to obtain suitable doses of less than 500mg.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use
Where analgesics are used long-term (>3 months) with administration every two days or more frequently, headache may develop or worsen. Headache induced by overuse of

analgesics (MOH medication-overuse headache) should not be treated by dose increase. In such cases, the use of analgesics should be discontinued in consultation with the doctor.
Care is advised in the administration of paracetamol to patients with alcohol dependency (see section 4.9), severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Label Warnings:
Do not exceed the recommended dose
If symptoms persist consult your doctor
Keep out of the reach and sight of children
Do not take with any other paracetamol-containing products.
Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.
or if leaflet present:
Immediate medical advice should be sought in the event of an overdose, even if you feel well.

4.5 Interaction with other medicinal products and other forms of interaction
• Anticoagulants - the effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding. Occasional doses have no significant effect.
• Metoclopramide – may increase speed of absorption of paracetamol.
• Domperidone – may increase speed of absorption of paracetamol.
• Colestyramine – may reduce absorption if given within one hour of paracetamol.
• Imatinib - restriction or avoidance of concomitant regular paracetamol use should be taken with imatinib.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostagladin effects of both NSAID and calcineurin inhibitor

Quinolone antibacterials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

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

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.

Cardiac glycosides: Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women indicates neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Breast-feeding

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding.

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. If diclofenac is used by a woman attempting to conceive, or during the 1st trimesters of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis

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 is contra-indicated during the third trimester of pregnancy.

Lactation

Like other NSAIDs, diclofenac passes into breast milk in small amounts. Therefore Diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant (see section 5.2 Pharmacokinetic properties).

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

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

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); Unknown: cannot be estimated from available data.
The following undesirable effects include those reported with other short-term or long-term use.

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leucopoenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.
Immune system disorders	
Rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare	Angioneurotic oedema (including face oedema).
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common	Headache, dizziness.
Rare	Somnolence, tiredness.
Very rare	Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.
Unknown	Confusion, hallucinations, disturbances of sensation malaise
Eye disorders	
Very rare	Visual disturbance, vision blurred, diplopia.
Unknown	Optic neuritis.
Ear and labyrinth disorders	

Common	Vertigo.
Very rare	Tinnitus, hearing impaired.
Cardiac disorders	
Uncommon*	Myocardial infarction, cardiac failure, palpitations, chest pain .
Unknown	Kounis syndrome
Vascular disorders	
Very rare	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare	Asthma (including dyspnoea).
Very rare	Pneumonitis.
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly).
Very rare	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.
Unknown	Ischaemic colitis
Hepatobiliary disorders	
Common	Transaminases increased.
Rare	Hepatitis, jaundice, liver disorder.
Very rare	Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common	Rash.
Rare	Urticaria
Very rare	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.
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

Diclofenac Potassium tablets contain the potassium salt of diclofenac, a non-steroidal compound with pronounced and clinically demonstrable analgesic, anti-inflammatory and anti-pyretic properties.
Diclofenac is a potent inhibitor of prostaglandin biosynthesis and a modulator of arachidonic acid release and uptake.
Diclofenac Potassium tablets have a rapid onset of action and are therefore suitable for the treatment of acute episodes of pain and inflammation.
Paracetamol has analgesic and antipyretic properties but it has no useful anti-inflammatory properties.
Paracetamol's effects are thought to be related to inhibition of prostaglandin synthesis.

5.2 Pharmacokinetic properties

Absorption
Paracetamol is readily absorbed from the gastrointestinal tract.
Distribution
Peak plasma concentrations occur about 10 to 60 minutes after oral doses. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk.
Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.
Biotransformation
It is metabolised in the liver. A minor hydroxylated metabolite 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 tissue damage.

Elimination
It is excreted in the urine, mainly as the glucuronide and sulfate conjugates. The elimination half-life varies from about 1 to 4 hours.

Absorption
Diclofenac is rapidly and completely absorbed from sugar-coated tablets. Food intake does not affect absorption.
Peak plasma concentration after one 50 mg sugar-coated tablet was 3.9 μmol/l after 20-60 minutes. The plasma concentrations show a linear relationship to the size of the dose.
Diclofenac undergoes first-pass metabolism and is extensively metabolised.

Distribution
Diclofenac is highly bound to plasma proteins (99.7%), chiefly albumin (99.4%)
Diclofenac was detected in a low concentration (100ng/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 (see section 4.6 Pregnancy and lactation).

Elimination
The total systemic clearance of diclofenac in plasma is 263 ± 56 ml/min (mean ± SD).
The terminal half-life in plasma is 1 – 2 hours.
Repeated oral administration of Diclofenac Potassium tablets for 8 days in daily doses of 50 mg t.d.s does not lead to accumulation of diclofenac in the plasma.
Approx. 60% of the dose administered is excreted in the urine in the form of metabolites, and less than 1% as unchanged substance. The remainder of the dose is eliminated as metabolites through the bile in the faeces.

Biotransformation
The biotransformation of diclofenac involves partly glucuronidation of the intact molecule but mainly single and multiple hydroxylation followed by glucuronidation.

Characteristics in patients
The age of the patient has no influence on the absorption, metabolism, or excretion of diclofenac.

5.3 Preclinical safety data
Relevant information on the safety of Diclofenac potassium tablets is included in other sections of the Summary of Product Characteristics.

6. Pharmaceutical particulars

6.1 List of excipients
Starch, Talc, Magnesium Stearate, Aerosil, Sodium Starch Glycolate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package and keep containers tightly closed.

6.5 Nature and contents of container
2x12 capsules

6.6 Special precautions for disposal and other handling
Not applicable.

7. Marketing authorisation holder
First Vadis Pharmaceuticals Limited,
Plot IN/2, Phase 2, Ext. Emene Industrial Layout,
Enugu-Nigeria

8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text
