VOTA-HANBET-B CAPLETS
VOTA-HANBET-B FORTE CAPLETS

This information is intended for use by health professionals

1. Name of the medicinal product

Vota-Hanbet-B Caplets
Vota-Hanbet-B Forte Caplets

2. Qualitative and quantitative composition

Vota-Hanbet B

Each film-coated caplet contains:
Diclofenac Sodium..... 50mg
Vitamin B_1 (Thiamine hydrochloride).....50mg
Vitamin B_6 (Pyridoxine hydrochloride)....100mg
Vitamin B_{12} (Cyanocobalamin).....100mcg

Vota-Hanbet B-Forte

Each film-coated caplet contains:
Diclofenac Sodium.....100mg
Vitamin B_1 (Thiamine hydrochloride).....100mg
Vitamin B_6 (Pyridoxine hydrochloride).....200mg
Vitamin B_{12} (Cyanocobalamin).....200mcg

3. Pharmaceutical form

Vota-Hanbet-B Tablets & Vota-Hanbet-B Forte Tablets is Oral Tablet, Light green, oblong tablet

4. Clinical particulars

4.1 Therapeutic indications

Musculoskeletal and Joint Disorder, inflammation, Pain, Neuralgia and Neuritis (Neuropathies).

4.2 Posology and method of administration

Posology

In adults, the dosage is one tablet of Vota-Hanbet B Caplets or half of Vota-Hanbet B Forte Caplets three times daily depending on the severity of the condition. The maintenance dose should be adjusted to the minimum that will provide continuous therapeutic control. The tablets should be swallowed whole, with or after a meal. The dosage in children is 2 mg per kilogram body mass daily calculated by Diclofenac. The maximum recommended daily dose for Diclofenac in any dosage form is 150 mg.

The dosage in children is 2 mg per kilogram body mass daily calculated by Diclofenac. Children under 3 years: Not recommended.

Elderly

Although the pharmacokinetics of Vota-Hanbet B Caplets & Vota-Hanbet B Forte Caplets 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.

Method of administration of Tablets

For oral administration

4.3 Contraindications

Vota-Hanbet B Caplets and Vota-Hanbet B-Forte Caplets are contra-indicated with hypersensitivity to its components. Avoid use in the presence of pepticulcer, pregnancy, lactation, hypersensitivity (e.g. asthma attacks) to acetylsalicylic acid or other NSAID agent. Severe disorders of liver function in hematopoietic disorders.

4.4 Special warnings and precautions for use

Gastro-intestinal disorders, including epigastric pain, eructation, nausea and vomiting may occur. Peptic ulceration and

gastro-intestinal bleeding have been reported. Other side-effects include vertigo, headache, skin rashes, pruritis, tinnitus, depression, drowsiness, nervousness, insomnia, irritability, agitation, minor hearing disorders, oedema, palpitations, blurred vision and other ocular reactions. Hypersensitivity reactions, abnormalities of liver function tests, impairment of renal function, agranulocytosis and thrombocytopenia have been observed. Dizziness, eczema, haemolytic anaemia may also occur.

It is advisable to perform blood counts in patients undergoing prolonged treatment.

Vota-Hanbet B Caplets and Vota-Hanbet B-Forte Caplets should be given with care to patients with cardiovascular disease, bleeding disorders, in those who are receiving coumarin anti-coagulants, and in patients with impaired hepatic or renal function.

Acute allergic reactions have been reported. Because of the possibility of cross-sensitivity due to structural relationships which exist among non-steroidal anti-inflammatory medicines, acute allergic reactions may be more likely to occur in patients who have exhibited allergic reactions to these compounds.

Allergic reactions which include angio-oedema, bronchospasm, urticaria, and anaphylactic reactions, have occurred.

In view of the product's inherent potential to cause fluid retention, heart failure may be pricipitated in some compromised patients.

Plasma concentrations are significantly decreased by the concomitant administration of therapeutic doses of aspirin.

When given together with preparations containing lithium or digoxin, diclofenac sodium may raise their plasma concentrations.

Concomitant administration of glucocorticoids or other non-steroidal anti-inflammatory agents may aggravate gastro-intestinal side-effects.

Concurrent administration with two or more non-steroidal anti-inflammatory agents may promote the occurrence of side-effects.

Should be used with caution in patients with asthma or bronchoconstriction.

Use carefully in elderly patients.

Decreased platelet aggregation with increased bleeding time may occur.

May increase the half-life of probenecid.

Use with care together with other protein-bound medicines e.g. Tolbutamide, Coumarin and Hydantoin.

4.5 Interaction with other medicinal products and other forms of interaction

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

Lithium: If used concomitantly, Voltarol may increase plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin: If used concomitantly, Voltarol may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of Voltarol 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.

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 periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity (see section 4.4 Special warnings and precautions for use).

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 (see section 4.4 Special warnings and precautions for use).

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4 Special warnings and precautions for use). 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 (see section 4.4 Special warnings and precautions for use). Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

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 (see section 4.4 Special warnings and precautions for use).

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of SSRI's may increase the risk of gastrointestinal bleeding (see section 4.4 Special warnings and precautions for use).

Antidiabetics: Clinical studies have shown that Voltarol can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of 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 treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increase. Cases of serious toxicity have been reported when methotrexate and NSAIDs, including diclofenac are given within 24

hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.
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.
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.

Pyridoxine may increase the peripheral metabolism of levodopa, reducing therapeutic efficacy of the latter drug. Therefore, patients with Parkinson's disease who are receiving treatment with plain levodopa should not take vitamin B6 in doses which greatly exceed the daily requirement. This does not apply when levodopa is combined with a peripheral decarboxylase inhibitor.

4.6 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 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 Voltarol is used by a woman attempting to conceive, or during the 1st trimester 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, Voltarol is contraindicated 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 .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

Toxic effects are unlikely since any excess vitamin B is excreted.

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 the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence,

Rare Very rare Unknown	anorexia. 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	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.
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).

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac over dosage. Over dosage can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, diarrhoea, dizziness, disorientation,

excitation, coma, drowsiness, tinnitus, fainting or convulsions. In the case of significant poisoning acute renal failure and liver damage are possible.
Therapeutic measures
Management of acute poisoning with NSAIDs, including diclofenac, essentially consists 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 haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to high protein binding 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.

Excess vitamin B is readily excreted, therefore no serious problems are anticipated for the administration of vitamin B in this form.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nonsteroidal anti-inflammatory drug (NSAID).

Diclofenac Rapid tablets contain the potassium salt of diclofenac, a nonsteroidal compound with pronounced and clinically demonstrable analgesic, anti-inflammatory and anti-pyretic properties.

Diclofenac is a potent inhibitor of prostaglandin bio-synthesis and modulator of arachidonic acid release and uptake.

Diclofenac Rapid tablets have a rapid onset of action and are therefore suitable for the treatment of acute episodes of pain and inflammation.

In migraine attacks Diclofenac Rapid has been shown to be effective in relieving the headache and in improving the accompanying symptom of nausea.

Diclofenac *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

5.2 Pharmacokinetic properties

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 (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 (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 Rapid for 8 days in daily doses of 50 mg t i d 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.

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 <10 ml/min the theoretical steady-state plasma levels of metabolites are about four times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

In the presence of impaired hepatic function (chronic hepatitis, non-decompensated cirrhosis) the kinetics and metabolism are the same as for patients without liver disease.

5.3 Preclinical safety data

Relevant information on the safety of Diclofenac Rapid is included in other sections of the Summary of Product Characteristics.

6. STORAGE

Store below 30°C. Protect from light and moisture. Keep out of reach of children.

7. MANUFACTURER

Shandong Xier Kangtai Pharmaceutical Co., Ltd.
Private Economy Garden, Xinyan Town, Yanzhou City, Shandong Province, China