Pain-*Aid* plus Gastro Safe Tablets*

پین۔ایڈ پلس ٹیبلٹس

COMPOSITION: *Each 50/200 tablet contains:* Diclofenac Sodium BP/USP....50 mg Misoprostol BP..... 200 mcg

Each 75/200 tablet contains: Diclofenac Sodium BP/USP.....75 mg Misoprostol BP.....200 mcg

DESCRIPTION: Pain-*Aid* plus is a combination product containing diclofenac sodium, a nonsteroidal anti-inflammatory drug and misoprostol, a gastrointestinal mucosal protective prostaglandin E1 analog. **Diclofenac sodium:** It is a phenylacetic acid derivative which is chemically described as 2-[(2, 6-dichlorophenyl) amino] benzeneacetic acid, monosodium salt. Its molecular formula is $C_{14}H_{10}Cl_2NO_2Na$ and its molecular weight is 318.14. **Misoprostol**: It is a synthetic oral prostaglandin E1 analog. Chemically it is described as (±)-methyl (13E)-11, 16-dihydroxy-16-methyl-9-oxoprost-13-enoate. The molecular formula is $C_{22}H_{38}O_5$ and its molecular weight is 382.5.

PHARMACOLOGY: *Pharmacodynamics:* **Diclofenac Sodium:** The mechanism of action of diclofenac sodium like other NSAIDs is not completely understood but may be related to prostaglandin synthetase inhibition. **Misoprostol:** It inhibits basal and nocturnal gastric acid secretion through a direct action on the parietal cell. Misoprostol also exerts a mucosal protecting effect that may contribute to its effectiveness in treating ulcers. *Pharmacokinetics:* **Diclofenac Sodium:** Peak plasma levels are achieved in 2 hours in fasting normal volunteers, with a range from 1 to 4 hours. Peak plasma levels of 1.5 mcg/mL are attained on average 2 hours after ingestion of 50 mg of diclofenac sodium. When diclofenac is taken with food, there is usually a delay in the onset of absorption of 1 to 4.5 hours. The extent of absorption of diclofenac, however, is not significantly affected by food intake. Clearance and volume of distribution are about 350 mL/min and 550 mL/kg, respectively. More than 99% of diclofenac is reversibly bound to human plasma albumin. As with other NSAIDs, diclofenac diffuses into and out of the synovial fluid. Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile. **Misoprostol:** Orally administered misoprostol is rapidly and extensively absorbed and undergoes rapid metabolism to its biologically active metabolite, misoprostol acid, which is thereafter quickly eliminated, with an elimination half-life of approximately 30 minutes. Food and antacids decrease the rate and extent of absorption. Approximately 70% of the administered dose is excreted in the urine, mainly as biologically inactive metabolites. Less than 1% of a dose is excreted in the urine as unchanged drug. It is unknown whether misoprostol crosses the placenta or is distributed in the breast milk. Since it can stimulate uterine contractions, it should not be given to pregnant women. The pharmacokinetics of diclofenac sodium/misoprostol are similar to the pharmacokinetics of the two individual components.

INDICATIONS: Pain-*Aid* plus 50 mg/200 mcg & 75 mg/200 mcg Tablets are indicated for acute and chronic treatment of the signs and symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute musculoskeletal disorders.

CONTRAINDICATIONS: Diclofenac sodium/Misoprostol combination is contraindicated in:

- Patients with known hypersensitivity to diclofenac sodium or to misoprostol or to other prostaglandins.
- Pregnant women as misoprostol can initiate uterine contractions leading to abortion.
- Patients in whom aspirin and other NSAIDs have induced symptoms of asthma, nasal polyps, angioedema or urticaria.
- Patients with active peptic ulceration or with its specific complications of recent bleeding and/or perforation or in other cases of gastrointestinal bleeding.
- Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
- Patients with severe renal, hepatic or heart failure.
- Lactating mothers.

POSSIBLE ADVERSE EFFECTS: The most common adverse effect encountered with NSAIDs is gastrointestinal, of which peptic ulcer with or without bleeding is the most severe. Other side effects encountered are: *Gastrointestinal:* Abdominal pain, flatulence, diarrhea, gall bladder disorder, glossitis, haematemesis, malena. *Hepatic:* Bilirubinaemia, abnormal hepatic functions, LDH increased, phosphatase alkaline increased and SGPT increased. *Renal:* Papillary necrosis *Gynaecological:* Menorrhagia, intermenstrual bleeding, dysmenorrhoea, leukorrhoea and vaginal bleeding. *CNS/Psychiatric:* Anorexia, anxiety, impaired concentration, headache, dry mouth, vertigo. *Dermatologic:* Angioedema, erythema multiforme, urticaria. *CVS:* Palpitation, syncope. *Special Senses:* Earache, tinnitus, eye pain. *Genitourinary:* Dysuria, abnormal urine. *Haematologic:* Leucopenia, thrombocytopenia. *Body as a Whole:* Hot flushes, malaise. *Respiratory:* Hyperventilation, increased sputum.

DRUG INTERACTIONS: *Digoxin:* Patients receiving digoxin with diclofenac sodium/misoprostol combination should be monitored for possible digoxin toxicity. *Antihypertensive Agents:* NSAIDs can inhibit the activity of antihypertensives including ACE Inhibitors. Thus caution should be taken when administering this combination with such agents. The use of an ACE-inhibitor or angiotensin receptor antagonist and an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time, increases the risk of renal impairment. *Warfarin:* The effects of warfarin on GI bleeding are synergistic, such that users of both drugs together have the risk of serious bleeding greater than users of either drug alone. *Anti-diabetics:* Marketing experiences report, changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac sodium that necessitated changes in the doses of such agents. *Methotrexate & Cyclosporine***:** Diclofenac sodium/misoprostol combination may increase serum concentrations of methotrexate and increase cyclosporine nephrotoxicity. *Diuretics:* Concomitant therapy of NSAIDs with potassium sparing diuretics may be associated with increased serum potassium levels. *Lithium:* Diclofenac decreases lithium renal clearance and increases lithium plasma levels. Therefore, Diclofenac

sodium/misoprostol should be administered with caution in patients receiving lithium.

WARNINGS: *Pregnant Women:* Because of the abortifacient property of misoprostol, diclofenac sodium/misoprostol combination is contraindicated for use in pregnant women. Misoprostol may cause miscarriage if given during pregnancy. Miscarriages may be incomplete which could lead to dangerous bleeding, hospitalization, surgery, infertility, maternal or fetal death. *Gastrointestinal Effects-Risk of Ulceration, Bleeding & Perforation:* Serious, potentially fatal gastrointestinal toxicity, such as bleeding, ulceration, and perforation, have been reported in patients receiving NSAID therapy, including diclofenac sodium/misoprostol combination. Therefore, physicians and patients should remain alert for ulceration, even in the absence of gastrointestinal symptoms. Patients at most risk of developing GI complications with NSAIDs are the elderly, patients with cardiovascular disease, patients using concomitant aspirin, or patients with a prior history of or active gastrointestinal disease such as ulceration, GI bleeding or inflammatory conditions. *Cardiovascular Thrombotic Events*: NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. To minimise the potential risk for an adverse cardiovascular event in patients treated with diclofenac sodium/misoprostol, especially those with cardiovascular risk factors, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. *Hypertension:* NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter. *Heart Failure:* Fluid retention and oedema have been observed in some patients taking NSAIDs, including diclofenac sodium/misoprostol combination. Therefore, diclofenac sodium/misoprostol combination should be used with caution in patients with a history of congestive heart failure or conditions predisposing to or worsened by fluid retention. *Hepatic Effects:* Diclofenac has been shown to produce elevations in one or more liver tests. These laboratory abnormalities may progress, remain unchanged, or may be transient with continued therapy and are usually reversible on cessation of therapy. During diclofenac sodium/misoprostol combination therapy, liver function should be monitored periodically. *Renal Effects:* As a class, NSAIDs have been associated with renal pathology such as papillary necrosis, glomerulitis and interstitial nephritis. Since diclofenac metabolites are excreted predominantly by the kidneys, patients with renal impairment should be monitored during diclofenac sodium/misoprostol combination therapy. *Haematologic Effects:* Patients on long-term treatment with NSAIDs including diclofenac sodium/misoprostol combination should have their hemoglobin or heamatocrit checked if they exhibit any signs or symptoms of anaemia. Diclofenac increases platelet aggregation time, prothrombin time and partial thromboplastin time. In patients with coagulation disorders or those receiving anticoagulants should be carefully monitored. *Skin Reactions:* NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens - Johnson syndrome (SJS), which can be fatal and occur without warning. Patients should be advised of the signs and symptoms of serious skin reactions. *Pre-existing Asthma:* Diclofenac sodium/misoprostol combination should be used with caution in patients with pre-existing asthma. *Lactation:* Diclofenac sodium/misoprostol combination should not be used by nursing mothers as both misoprostol acid & diclofenac are excreted in breast milk. *Use in Children:* Safety and effectiveness of diclofenac sodium/misoprostol combination in children below the age of 18 years have not been established.

DOSAGE & ADMINISTRATION: *Osteoarthritis:* The recommended dosage is Pain-*Aid* plus 50 mg/200 mcg Tablets thrice a day. For patients who experience intolerance Pain-*Aid* plus 75 mg/200 mcg or 50 mg/200 mcg tablets 2 times a day can be used. *Rheumatoid Arthritis:* The recommended dosage is Pain-*Aid* plus 50 mg/200 mcg tablets thrice a day or 4 times a day. For patients who experience intolerance Pain-*Aid* plus 75 mg/200 mcg or 50 mg/200 mcg tablets 2 times a day can be used. *Ankylosing Spondylitis:* The recommended dosage is Pain-*Aid* plus 50 mg/ 200 mcg tablets 3 to 4 times a day. *Acute Musculoskeletal Disorders:* The recommended dosage is Pain-*Aid* plus 50 mg/ 200 mcg 2 to 3 times a day. Tablets should be swallowed whole, not chewed or crushed.

SPECIAL INSTRUCTION TO THE PHYSICIAN: *Overdosage:* Treatment of diclofenac sodium/misoprostol combination overdose should be symptomatic and supportive. Induced diuresis may be beneficial because diclofenac and misoprostol metabolites are excreted in the urine. The use of oral activated charcoal may help to reduce the absorption of diclofenac and misoprostol. Activated charcoal is most effective when administered within 1-hour of ingestion. *Note on Misoprostol:* The total dose of misoprostol should not exceed 800 mcg/day, and no more than 200 mcg of misoprostol should be administered at any one time. Doses of diclofenac higher than 150 mg/day in osteoarthritis or higher than 225 mg/day in rheumatoid arthritis are not recommended.

STORAGE/PRECAUTIONS: Store in a cool, dry and dark place between 15-30 °C. Keep all medicines out of the children's reach.

PRESENTATION: Pain-*Aid* plus 50 mg/200 mcg Tablets and Pain-*Aid* plus 75 mg/200 mcg Tablets are available in packing containing 20 tablets, respectively. **Scotmann Specs.*

عمومی خوراک: ڈاکٹر کی ہدایت کے مطابق۔ احتیاط: دوا صرف مستند ڈاکٹر کے زیرِ ہدایت استعمال کریں۔ روشنی، نمی اور گرمی سے بچائیں۔ 15 سے 30 ڈگری سینٹی گریڈ کے درمیان محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

Complete Medical Information available only for doctors on request.

Manufactured by: **SCOTMANN PHARMACEUTICALS**
5-D, I-10/3 Industrial Area, Islamabad-Pakistan
www.scotmann.com