For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

DOMSTAL NP

1. Generic Name

Domperidone and Naproxen Sodium Tablets

2. Qualitative and quantitative composition

DOMSTAL NP 250

Each film coated tablet contains:
Domperidone Maleate I.P. equivalent to Domperidone……10 mg
Naproxen Sodium U.S.P. ……..275 mg
equivalent to Naproxen...……...250 mg
Excipients……...q.s.
Colours: Red Oxide of Iron and Titanium Dioxide I.P.

The excipients used are Lactose anhydrous, Microcrystalline cellulose, Starch, Maleic Acid, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Talcum. Magnesium Stearate, Colloidal Silicon dioxide, Sodium Starch Glycolate, Polyvinyl Alcohol, Glycerol Monostearate, Polysorbate 80, Triacetin, Modified Starch, Titanium Dioxide and Red Oxide of Iron.

DOMSTAL NP 500

Each film coated tablet contains:
Domperidone Maleate I.P. equivalent to Domperidone……10 mg
Naproxen Sodium U.S.P. ……..550 mg
equivalent to Naproxen...……...500 mg
Excipients……...q.s.

Colours: Red Oxide of Iron and Titanium Dioxide I.P.

The excipients used are Lactose anhydrous, Microcrystalline cellulose, Starch, Maleic Acid, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Talcum. Magnesium Stearate, Colloidal Silicon dioxide, Sodium Starch Glycolate, Polyvinyl Alcohol, Glycerol Monostearate, Polysorbate 80, Triacetin, Modified Starch, Titanium Dioxide and Red Oxide of Iron.

3. Dosage form and strength

Dosage Form: Film coated tablets

Strength: Naproxen Sodium eq to Naproxen - 250 mg/500 mg and Domperidone – 10mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of migraine.

4.2 Posology and method of administration

General Dosing Instructions

Carefully consider the potential benefits and risks of DOMSTAL NP and other treatment options before deciding to use DOMSTAL NP. Use the lowest effective dose for the

shortest duration consistent with individual patient treatment goals (see *Special warnings and precautions for use*).

After observing the response to initial therapy with DOMSTAL NP, the dose and frequency should be adjusted to suit an individual patient's needs.

Other Naproxen-containing products should not be used concomitantly since they all circulate in the plasma as the naproxen anion.

Hepatic Impairment

DOMSTAL NP is contraindicated in moderate or severe hepatic impairment (see *Contraindications*). Dose modification in mild hepatic impairment is however not needed (see *Pharmacokinetic properties*).

Renal Impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration, the dosing frequency of DOMSTAL NP should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced. Such patients on prolonged therapy should be reviewed regularly (see *Special warnings and precautions for use* and *Pharmacokinetic properties*) Dosage: As directed by the Physician.

4.3 Contraindications

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to naproxen, domperidone or any components of the drug product (see *Special warnings and precautions for use*).
- 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 (see *Special warnings and precautions for use)*.
- In the setting of coronary artery bypass graft (CABG) surgery (see *Special warnings and precautions for use)*
- Prolactin-releasing pituitary tumour (prolactinoma).
- When stimulation of the gastric motility could be harmful e.g in patients with gastrointestinal haemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment (see *Pharmacokinetic properties*).
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure (see *Special warnings and precautions for use*).
- Co-administration with QT-prolonging drugs, at the exception of apomorphine (see *Special warnings and precautions for use* and *Drug interactions*).
- Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects) (see *Drug interactions*).

4.4 Special warnings and precautions for use

DOMPERIDONE

Cardiovascular effects

Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. As per reported data, during post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors (see *Undesirable effects*).

Reported epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see *Undesirable effects*). A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors.

Domperidone should be used at the lowest effective dose in adults and adolescents 12 years of age and older.

Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia (see *Contraindications*). Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic risk.

Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia and the patients should consult their physician.

Patients should be advised to promptly report any cardiac symptoms.

Use with apomorphine

Domperidone is contra-indicated with QT prolonging drugs including apomorphine, unless the benefit of the co-administration with apomorphine outweighs the risks.

Renal impairment

The elimination half-life of domperidone is prolonged in severe renal impairment. For repeated administration, the dosing frequency of DOMSTAL NP should be reduced depending on the severity of the impairment. The dose may also need to be reduced.

NAPROXEN

Cardiovascular Thrombotic Events

Reportedly, clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or

risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as naproxen, increases the risk of serious gastrointestinal (GI) events (see *Special warnings and precautions for use*).

Status Post Coronary Artery Bypass Graft (CABG) Surgery
Two large, reported controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG (see *Contraindications*).

Post-MI Patients
Reportedly, observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of DOMSTAL NP in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If DOMSTAL NP is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including naproxen, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs.

Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation
Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared

to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue DOMSTAL NP until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding (see *Drug Interactions*).

Hepatotoxicity

Elevations of ALT or AST [three or more times the upper limit of normal (ULN)] have been reported in approximately 1% of NSAID-treated patients in reported clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including naproxen.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flulike" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue DOMSTAL NP and perform a clinical evaluation of the patient.

Hypertension

NSAIDs, including Naproxen, can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs (see *Drug Interactions*).

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

Heart Failure and Edema

Reportedly, the Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in

hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of naproxen may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) (see *Drug Interactions).*

Avoid the use of DOMSTAL NP in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If DOMSTAL NP is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Renal Toxicity and Hyperkalemia

Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from reported controlled clinical studies regarding the use of Naproxen in patients with advanced renal disease. The renal effects of DOMSTAL NP may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating DOMSTAL NP. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of DOMSTAL NP (see *Drug Interactions*). Avoid the use of DOMSTAL NP in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If DOMSTAL NP is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemichypoaldosteronism state.

Anaphylactic Reactions

Naproxen has been associated with anaphylactic reactions in patients with and without known hypersensitivity to naproxen and in patients with aspirin-sensitive asthma (see *Contraindications* and *Special warnings and precautions for use*).

Seek emergency help if an anaphylactic reaction occurs.

Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs.

Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, DOMSTAL NP is contraindicated in patients with this form of aspirin sensitivity (see *Contraindications*). When DOMSTAL NP is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

Serious Skin Reactions

NSAIDs, including Naproxen, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of DOMSTAL NP at the first appearance of skin rash or any other sign of hypersensitivity. DOMSTAL NP is contraindicated in patients with previous serious skin reactions to NSAIDs (see *Contraindications*).

Premature Closure of Fetal Ductus Arteriosus

Naproxen may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including Naproxen in pregnant women starting at 30 weeks of gestation (third trimester) (see *Use in Specific Populations*).

Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with DOMSTAL NP has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including Naproxen, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin and other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding (see *Drug Interactions*).

Masking of Inflammation and Fever

The pharmacological activity of Naproxen in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

Long-Term Use and Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically (see *Special warnings and precautions for use*).

Patients with initial hemoglobin values of 10g or less who are to receive long-term therapy should have hemoglobin values determined periodically.

Because of adverse eye findings in reported animal studies with drugs of this class, it is recommended that ophthalmic studies be carried out if any change or disturbance in vision occurs.

Excipients

The film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Drugs interactions

DOMPERIDONE

The main metabolic pathway of domperidone is through CYP3A4. Reported i*n vitro* data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone.

Increased risk of occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions.

Concomitant use of the following substances is contraindicated

QTc prolonging medicinal products

- anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine)
- anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol)
- certain anti-psychotics (e.g., haloperidol, pimozide, sertindole)
- certain anti-depressants (e.g., citalopram, escitalopram)
- certain antibiotics (e.g. , erythromycin, levofloxacin, moxifloxacin, spiramycin)
- certain antifungal agents (e.g., pentamidine)
- certain antimalarial agents (in particular halofantrine, lumefantrine)
- certain gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- certain antihistaminics (e.g., mequitazine, mizolastine)
- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicines (e.g., bepridil, diphemanil, methadone)

(see *Contraindications*)

- apomorphine, unless the benefit of the co-administration outweighs the risks, and only if the recommended precautions for co-administration are strictly fulfilled.

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e.:

- protease inhibitors
- systemic azole antifungals
- some macrolides (erythromycin, clarithromycin, telithromycin) (see *Contraindications*)

Concomitant use of the following substances is not recommended

Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides.

Concomitant use of the following substances requires caution in use

Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-interval prolongation: azithromycin and roxithromycin (clarithromycin is contra-indicated as it is a potent CYP3A4 inhibitor).

The above list of substances is representative and not exhaustive.

Reportedly, separate *in vivo pharmacokinetic/pharmacodynamic* interaction studies with oral ketoconazole or oral erythromycin in healthy subjects confirmed a marked inhibition of domperidone's CYP3A4 mediated first pass metabolism by these drugs.

With the combination of oral domperidone 10mg four times daily and ketoconazole 200mg twice daily, a mean QTc prolongation of 9.8 msec was seen over the observation period, with changes at individual time points ranging from 1.2 to 17.5 msec. With the combination of domperidone 10mg four times daily and oral erythromycin 500mg three times daily, mean QTc over the observation period was prolonged by 9.9 msec, with changes at individual time points ranging from 1.6 to 14.3 msec. Both the C_{max} and AUC of domperidone at steady state were increased approximately three-fold in each of these interaction studies. In these studies domperidone monotherapy at 10mg given orally four times daily resulted in increases in mean QTc of 1.6 msec (ketoconazole study) and 2.5 msec (erythromycin study), while ketoconazole monotherapy (200mg twice daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

NAPROXEN

Clinically Significant Drug Interactions with naproxen are presented in the table below:

Drugs That Interfere with Hemostasis	
Clinical Impact:	Naproxen and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of naproxen and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. Serotonin release by platelets plays an important role in hemostasis. Reported case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of DOMSTAL NP with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding (see *Special warnings and precautions for use).*
Aspirin	

Clinical Impact:	Reported controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone (see *Special warnings and precautions for use).*
Intervention:	Concomitant use of DOMSTAL NP and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding (see *Special warnings and precautions for use).* Naproxen is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	During concomitant use of DOMSTAL NP and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. During concomitant use of DOMSTAL NP and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function (see *Special warnings and precautions for use).* When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	Reportedly, clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.

Intervention:	During concomitant use of DOMSTAL NP with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects (see *Special warnings and precautions for use).*
Digoxin	
Clinical Impact:	The concomitant use of naproxen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin
Intervention:	During concomitant use of DOMSTAL NP and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of DOMSTAL NP and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of DOMSTAL NP and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of DOMSTAL NP and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of DOMSTYAL NP and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	

Clinical Impact:	Concomitant use of naproxen with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy (see *Special warnings and precautions for use).*
Intervention:	The concomitant use of naproxen with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of DOMSTAL NP and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity.
Intervention:	During concomitant use of DOMSTAL NP and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
Antacids and Sucralfate	
Clinical Impact:	Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the absorption of naproxen.
Intervention:	Concomitant administration of antacids such as magnesium oxide or aluminum hydroxide, and sucralfate with DOMSTAL NP is not recommended.
Cholestyramine	
Clinical Impact:	Concomitant administration of cholestyramine can delay the absorption of naproxen.
Intervention:	Concomitant administration of cholestyramine with DOMSTAL NP is not recommended.
Probenecid	
Clinical Impact:	Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

Intervention:	Patients simultaneously receiving DONSTAL NP and probenecid should be observed for adjustment of dose if required.
Other albumin-bound drugs	
Clinical Impact:	Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs, and aspirin.
Intervention:	Patients simultaneously receiving DOMSTAL NP and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

Drug/Laboratory Test Interactions

Bleeding times	
Clinical Impact:	Naproxen may decrease platelet aggregation and prolong bleeding time.
Intervention:	This effect should be kept in mind when bleeding times are determined.
Porter-Silber test	
Clinical Impact:	The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-dinitrobenzene used in this assay.
Intervention:	Although 17-hydroxy-corticosteroid measurements (PorterSilber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.
Urinary assays of 5-hydroxy indoleacetic acid (5HIAA)	
Clinical Impact:	Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).
Intervention:	This effect should be kept in mind when urinary 5-hydroxy indoleacetic acid is determined.

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

DOMPERIDONE

Pregnancy

There are limited post-marketing data on the use of domperidone in pregnant women. Reported studies in animals have shown reproductive toxicity at maternally toxic doses (see *Animal Toxicology or Pharmacology*). Domperidone should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Breast-feeding

Domperidone is excreted in human milk and breast-fed infants receive less than 0.1 % of the maternal weight-adjusted dose. Occurrence of adverse effects, in particular cardiac effects cannot be excluded after exposure via breast milk. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from domperidone therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants.

NAPROXEN Pregnancy

Risk Summary

Use of NSAIDs, including naproxen, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including naproxen, in pregnant women starting at 30 weeks of gestation (third trimester).

There are no adequate and well-controlled studies of naproxen in pregnant women. Reported data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In reported animal reproduction studies in rats, rabbits and mice no evidence of teratogenicity or fetal harm when naproxen was administered during the period of organogenesis at doses 0.13, 0.26, and 0.6 times the maximum recommended human daily dose of 1500 mg/day, respectively. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In reported animal studies, administration of prostaglandin synthesis inhibitors such as naproxen, resulted in increased pre-and postimplantation loss.

Clinical Considerations

Labor or Delivery

There are no studies on the effects of naproxen during labor or delivery. In reported animal studies, NSAIDS, including naproxen, inhibits prostaglandin synthesis, causes delayed parturition, and increases the incidence of stillbirth.

Data

Human Data

There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor, there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus, and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction, and abnormal prostaglandin E

levels in preterm infants. Because of the known effects of nonsteroidal antiinflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly starting at 30-weeks of gestation, or third trimester) should be avoided.

Animal data

Reportedly, reproduction studies have been performed in rats at 20 mg/kg/day (0.13 times the maximum recommended human daily dose of 1500 mg/day based on body surface area comparison), rabbits at 20 mg/kg/day (0.26 times the maximum recommended human daily dose, based on body surface area comparison), and mice at 170 mg/kg/day (0.6 times the maximum recommended human daily dose based on body surface area comparison) with no evidence of impaired fertility or harm to the fetus due to the drug. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In reported animal studies, administration of prostaglandin synthesis inhibitors such as naproxen, resulted in increased pre-and post-implantation loss.

Lactation

Risk Summary

The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DOMSTAL NP and any potential adverse effects on the breastfed infant from the same or from the underlying maternal condition.

Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including naproxen, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including naproxen, in women who have difficulties conceiving or who are undergoing investigation of infertility.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 2 years have not been established. Pediatric dosing recommendations for polyarticular juvenile idiopathic arthritis are based on well-controlled studies. Reportedly, there are no adequate effectiveness or dose-response data for other pediatric conditions, but the experience in polyarticular juvenile idiopathic arthritis and other use experience have established that single doses of 2.5 to 5 mg/kg as naproxen suspension, with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age.

Geriatric Use

The hepatic and renal tolerability of long-term naproxen administration was studied in two reported double-blind clinical trials involving 586 patients. Of the patients studied, 98 patients were age 65 and older and 10 of the 98 patients were age 75 and older. Naproxen was administered at doses of 375 mg twice daily or 750 mg twice daily for up to 6 months. Transient abnormalities of laboratory tests assessing hepatic and renal function were noted in some patients, although there were no differences noted in the occurrence of abnormal values among different age groups.

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects (see *Special warnings and precautions for use*).

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. The clinical significance of this finding is unclear, although it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some elderly patients. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

Experience indicates that geriatric patients may be particularly sensitive to certain adverse effects of nonsteroidal anti-inflammatory drugs. Elderly or debilitated patients seem to tolerate peptic ulceration or bleeding less well when these events do occur. Most spontaneous reports of fatal GI events are in the geriatric population (see *Special warnings and precautions for use*).

Naproxen is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see *Pharmacokinetic properties*). Geriatric patients may be at a greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of nonsteroidal anti-inflammatory drugs (see *Special warnings and precautions for use*).

Hepatic Impairment

Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose (see *Pharmacokinetic properties*).

Renal Impairment

Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance <30 mL/min) (see *Special warnings and precautions for use* and *Pharmacokinetic properties*).

4.7 Effects on ability to drive and use machines

Domperidone has no or negligible influence on the ability to drive and use machines.

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs like naproxen. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

DOMPERIDONE

Tabulated list of adverse reactions

Reportedly, the safety of domperidone was evaluated in clinical trials and in post marketing experience. The clinical trials included 1275 patients with dyspepsia, gastrooesophageal reflux disorder (GORD), Irritable Bowel Syndrome (IBS), nausea and vomiting or other related conditions in 31 double-blind, placebo-controlled studies. All patients were at least 15 years old and received at least one dose of domperidone (domperidone base). The median total daily dose was 30 mg (range 10 to 80 mg), and median duration of exposure was 28 days (range 1 to 28 days). Studies in diabetic gastroparesis or symptoms secondary to chemotherapy or parkinsonism were excluded.

The following terms and frequencies are applied: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), Where frequency can not be estimated from clinical trials data, it is recorded as "Not known".

System Organ Class	**Adverse Drug Reaction Frequency**		
	Common	**Uncommon**	**Not known**
Immune system disorders			Anaphylactic reaction (including anaphylactic shock)
Psychiatric disorders		Loss of libido Anxiety	Agitation Nervousness
Nervous system disorders		Somnolence Headache	Convulsion Extrapyramidal disorder
Eye disorders			Oculogyric crisis
Cardiac disorders			Ventricular arrhythmias Sudden cardiac death QTc prolongation Torsade de Pointes

Gastrointestinal disorders	Dry mouth	Diarrhoea	
Skin and subcutaneous tissue disorder		Rash Pruritus	Urticaria Angioedema
Renal and urinary disorders			Urinary retention
Reproductive system and breast disorders		Galactorrhoea Breast pain Breast tenderness	Gynaecomastia Amenorrhoea
General disorders and administration site conditions		Asthenia	
Investigations			Liver function test abnormal Blood prolactin increased

In 45 studies where domperidone was used at higher dosages, for longer duration and for additional indications including diabetic gastroparesis, the frequency of adverse events (apart from dry mouth) was considerably higher. This was particularly evident for pharmacologically predictable events related to increased prolactin. In addition to the reactions listed above, akathisia, breast discharge, breast enlargement, breast swelling, depression, hypersensitivity, lactation disorder, and irregular menstruation were also noted.

NAPROXEN

The following adverse reactions are discussed in greater detail in *Special warnings and precautions for use*

- Cardiovascular Thrombotic Events
- GI Bleeding, Ulceration, and Perforation
- Hepatotoxicity
- Hypertension
- Heart Failure and Edema
- Renal Toxicity and Hyperkalemia
- Anaphylactic Reactions
- Serious Skin Reactions
- Hematologic Toxicity

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions reported in published controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, reactions in patients treated chronically were reported 2 to 10 times more frequently than they were in shortterm studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those taking 750 mg naproxen.

Reportedly, in controlled clinical trials with about 80 pediatric patients and in wellmonitored, open-label studies with about 400 pediatric patients with polyarticular juvenile idiopathic arthritis treated with naproxen, the incidence of rash and prolonged bleeding times were greater, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in pediatric patients than in adults.

In patients taking naproxen in clinical trials, the most frequently reported adverse experiences in approximately 1% to 10% of patients were:

Gastrointestinal (GI) Experiences, including: heartburn*, abdominal pain*, nausea*, constipation*, diarrhea, dyspepsia, stomatitis

Central Nervous System: headache*, dizziness*, drowsiness*, lightheadedness, vertigo

Dermatologic: pruritus (itching)*, skin eruptions*, ecchymoses*, sweating, purpura

Special Senses: tinnitus*, visual disturbances, hearing disturbances

Cardiovascular: edema*, palpitations

General: dyspnea*, thirst

*Incidence of reported reaction between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

In patients taking NSAIDs, the following adverse experiences have also been reported in approximately 1% to 10% of patients.

Gastrointestinal (GI) Experiences, including: flatulence, gross bleeding/perforation, GI ulcers (gastric/duodenal), vomiting

General: abnormal renal function, anemia, elevated liver enzymes, increased bleeding time, rashes

The following are additional adverse experiences reported in <1% of patients taking naproxen during clinical trials.

Gastrointestinal: pancreatitis, vomiting

Hepatobiliary: jaundice

Hemic and Lymphatic: melena, thrombocytopenia, agranulocytosis

Nervous System: inability to concentrate

Dermatologic: skin rashes

Postmarketing Experience

The following adverse reactions have been identified during post approval use of naproxen. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following are additional adverse experiences reported in <1% of patients taking naproxen during reported clinical trials and through post marketing reports. Those adverse reactions observed through post marketing reports are italicized.

Body as a Whole: anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever)

Cardiovascular: congestive heart failure, vasculitis, hypertension, pulmonary edema

Gastrointestinal: inflammation, bleeding (sometimes fatal, particularly in the elderly), ulceration, perforation and obstruction of the upper or lower gastrointestinal tract. Esophagitis, stomatitis, hematemesis, colitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease).

Hepatobiliary: abnormal liver function tests, hepatitis (some cases have been fatal)

Hemic and Lymphatic: eosinophilia, leucopenia, granulocytopenia, hemolytic anemia, aplastic anemia

Metabolic and Nutritional: hyperglycemia, hypoglycaemia

Nervous System: depression, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction, convulsions

Respiratory: eosinophilic pneumonitis, asthma

Dermatologic: alopecia, urticaria, toxic epidermal necrolysis, erythema multiforme, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, systemic lupus erythematoses, bullous reactions, including Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.

Special Senses: hearing impairment, corneal opacity, papillitis, retrobulbar optic neuritis, papilledema

Urogenital: glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis, raised serum creatinine

Reproduction (female): infertility

In patients taking NSAIDs, the following adverse experiences have also been reported in <1% of patients.

Body as a Whole: fever, infection, sepsis, anaphylactic reactions, appetite changes, death

Cardiovascular: hypertension, tachycardia, syncope, arrhythmia, hypotension, myocardial infarction

Gastrointestinal: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, glossitis, eructation

Hepatobiliary: hepatitis, liver failure

Hemic and Lymphatic: rectal bleeding, lymphadenopathy, pancytopenia

Metabolic and Nutritional: weight changes

Nervous System: anxiety, asthenia, confusion, nervousness, paresthesia, somnolence, tremors, convulsions, coma, Hallucinations

Respiratory: asthma, respiratory depression, pneumonia

Dermatologic: exfoliative dermatitis

Special Senses: blurred vision, conjunctivitis

Urogenital: cystitis, dysuria, oliguria/polyuria, proteinuria

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
https://torrentpharma.com/index.php/site/info/adverse_event_reporting

By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms

Symptoms of domperidone over dosage may include agitation, altered consciousness, convulsions, disorientation, somnolence and extrapyramidal reactions.

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare (see *Special warnings and precautions for use*). Because naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced convulsions, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening (see *Special warnings and precautions for use*).

Treatment

There is no specific antidote to domperidone and naproxen, but in the event of overdose, standard symptomatic treatment should be given immediately. Gastric lavage as well as the administration of activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage), may be useful. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Close medical supervision and supportive therapy is recommended.

Anticholinergic, anti-parkinson drugs may be helpful in controlling the extrapyramidal reactions.

Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding of naproxen.

5. Pharmacological properties

5.1 Mechanism of Action

DOMPERIDONE

Pharmacotherapeutic Group: Propulsives, ATC code: A03F A03

Domperidone is a dopamine antagonist with anti-emetic properties, Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors.

NAPROXEN

Naproxen has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of naproxen, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Naproxen is a potent inhibitor of prostaglandin synthesis in vitro. Naproxen concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because naproxen is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

5.2 Pharmacodynamic properties

DOMPERIDONE

Reported studies in man have shown oral domperidone to increase lower oesophaegeal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

In accordance with ICH—E14 guidelines, a thorough QT study was performed. This study included a placebo, an active comparator and a positive control and was conducted in healthy subjects with up to 80 mg per day 10 or 20 mg administered 4 times a day of domperidone. This study found a maximal difference of QTc between domperidone and placebo in LS-means in the change from baseline of 3.4 msec for 20 mg domperidone administered 4 times a day on Day 4. The 2-sided 90 % CI (1.0 to 5.9 msec) did not exceed 10 msec. No clinically relevant QTc effects were observed in this study when domperidone was administered at up to 80 mg/day (i.e., more than twice the maximum recommended dosing).

However, two previous drug-drug interaction studies showed some evidence of QTc prolongation when domperidone was administered as monotherapy (10 mg 4 times a day).The largest time-matched mean difference of QTcF between domperidone and

placebo was 5.4 msec (95 % CI: -1.7 to 12.4) and 7.5 msec (95 % CI: 0.6 to 14.4), respectively.

NAPROXEN

Reportedly, naproxen has been studied in patients with rheumatoid arthritis, osteoarthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, tendonitis and bursitis, and acute gout. Improvement in patients treated for rheumatoid arthritis was demonstrated by a reduction in joint swelling, a reduction in duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and patient, and by increased mobility as demonstrated by a reduction in walking time. Generally, response to naproxen has not been found to be dependent on age, sex, severity or duration of rheumatoid arthritis.

In patients with osteoarthritis, the therapeutic action of naproxen has been shown by a reduction in joint pain or tenderness, an increase in range of motion in knee joints, increased mobility as demonstrated by a reduction in walking time, and improvement in capacity to perform activities of daily living impaired by the disease.

In a reported clinical trial comparing standard formulations of naproxen 375 mg twice a day (750 mg a day) vs 750 mg twice a day (1500 mg/day), 9 patients in the 750 mg group terminated prematurely because of adverse events. Nineteen patients in the 1500 mg group terminated prematurely because of adverse events. Most of these adverse events were gastrointestinal events.

In clinical studies in patients with rheumatoid arthritis, osteoarthritis, and polyarticular juvenile idiopathic arthritis, naproxen has been shown to be comparable to aspirin and indomethacin in controlling the aforementioned measures of disease activity, but the frequency and severity of the milder gastrointestinal adverse effects (nausea, dyspepsia, heartburn) and nervous system adverse effects (tinnitus, dizziness, lightheadedness) were less in naproxen-treated patients than in those treated with aspirin or indomethacin.

In patients with ankylosing spondylitis, naproxen has been shown to decrease night pain, morning stiffness and pain at rest. In double-blind studies the drug was shown to be as effective as aspirin, but with fewer side effects.

In patients with acute gout, a favorable response to naproxen was shown by significant clearing of inflammatory changes (e.g., decrease in swelling, heat) within 24 to 48 hours, as well as by relief of pain and tenderness.

Naproxen has been studied in patients with mild to moderate pain secondary to postoperative, orthopedic, postpartum episiotomy and uterine contraction pain and dysmenorrhea. Onset of pain relief can begin within 1 hour in patients taking naproxen and within 30 minutes in patients taking naproxen sodium. Analgesic effect was shown by such measures as reduction of pain intensity scores, increase in pain relief scores, decrease in numbers of patients requiring additional analgesic medication, and delay in time to remedication. The analgesic effect has been found to last for up to 12 hours.

Naproxen may be used safely in combination with gold salts and/or corticosteroids; however, in controlled clinical trials, when added to the regimen of patients receiving corticosteroids, it did not appear to cause greater improvement over that seen with corticosteroids alone. Whether naproxen has a “steroid-sparing” effect has not been adequately studied. When added to the regimen of patients receiving gold salts, naproxen did result in greater improvement. Its use in combination with salicylates is

not recommended because there is evidence that aspirin increases the rate of excretion of naproxen and data are inadequate to demonstrate that naproxen and aspirin produce greater improvement over that achieved with aspirin alone. In addition, as with other NSAIDs, the combination may result in higher frequency of adverse events than demonstrated for either product alone.

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In Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1000 mg of naproxen has been demonstrated to cause statistically significantly less gastric bleeding and erosion than 3250 mg of aspirin.

5.3 Pharmacokinetic properties

DOMPERIDONE

Absorption

Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1hr after dosing. The C_{max} and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. A 2- to 3-fold accumulation of domperidone AUC was observed with repeated four times daily (every 5 hr) dosing of domperidone for 4 days.

The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone's bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

Distribution

Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/ml after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 9193% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of drug cross the placenta in rats.

Metabolism

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Urinary and faecal excretions amount to 31 and 66% of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of faecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7-9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

Hepatic impairment

In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and C_{max} of domperidone is 2.9- and 1.5-fold higher, respectively, than in healthy subjects. The unbound fraction is increased by 25%, and the terminal elimination half-life is prolonged from 15 to 23 hours. Subjects with mild hepatic impairment have a somewhat lower systemic exposure than healthy subjects based on C_{max} and AUC, with no change in protein binding or terminal half-life. Subjects with severe hepatic impairment were not studied. Domperidone is contraindicated in patients with moderate or severe hepatic impairment (see *Contraindications*).

Renal impairment

In subjects with severe renal insufficiency (creatinine clearance <30ml/min/1.73m^2) the elimination half-life of domperidone is increased from 7.4 to 20.8 hours, but plasma drug levels are lower than in healthy volunteers. Since very little unchanged drug (approximately 1%) is excreted *via* the kidneys, it is unlikely that the dose of a single administration needs to be adjusted in patients with renal insufficiency.

However, on repeated administration, the dosing frequency should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced.

Paediatric population

No pharmacokinetic data are available in the paediatric population.

NAPROXEN

Naproxen and naproxen sodium are rapidly and completely absorbed from the gastrointestinal tract with an in vivo bioavailability of 95%.

Absorption

After administration of naproxen, peak plasma levels are attained in 2 to 4 hours.

Antacid Effects

When naproxen was given as a single dose with antacid (54 mEq buffering capacity), the peak plasma levels of naproxen were unchanged, but the time to peak was reduced (mean T_{max} fasted 5.6 hours, mean T_{max} with antacid 5 hours), although not significantly (see *Drug Interactions*).

Food Effects

When naproxen was given as a single dose with food, peak plasma levels in most subjects were achieved in about 12 hours (range: 4 to 24 hours). Residence time in the small intestine until disintegration was independent of food intake. The presence of food prolonged the time the tablets remained in the stomach, time to first detectable serum naproxen levels, and time to maximal naproxen levels (T_{max}), but did not affect peak naproxen levels (C_{max}).

Distribution

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough C_{ss} 36.5, 49.2 and 56.4 mg/L with 500, 1000 and 1500 mg daily doses of naproxen, respectively). The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma (see *Use in Specific Populations*).

Elimination

Metabolism

Naproxen is extensively metabolized in the liver to 6-0-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Both naproxen and 6-0desmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites.

Excretion

The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (<1%), 6-0-desmethyl naproxen (<1%) or their conjugates (66% to 92%). The plasma half-life of the naproxen anion in humans ranges from 12 to 17 hours. The corresponding half-lives of both naproxen's metabolites and conjugates are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen clearance from the plasma. Small amounts, 3% or less of the administered dose, are excreted in the feces. In patients with renal failure metabolites may accumulate (see *Specal warnings and precautions for use*).

Specific Populations

Pediatric:

In pediatric patients aged 5 to 16 years with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen suspension (see *Dosage and Administration*) were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in pediatric and adult patients. Pharmacokinetic studies of naproxen were not performed in pediatric patients younger than 5 years of age. Pharmacokinetic parameters appear to be similar following administration of naproxen suspension or tablets in pediatric patients.

Geriatric:

Reported studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly, although the unbound fraction is <1% of the total naproxen concentration. Unbound trough naproxen concentrations in elderly subjects have been reported to range from 0.12% to 0.19% of total naproxen concentration, compared with 0.05% to 0.075% in younger subjects.

Hepatic Impairment:

Naproxen pharmacokinetics has not been determined in subjects with hepatic insufficiency.

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased.

Renal Impairment:

Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment.

Drug Interaction Studies

Aspirin: When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 1 for clinically significant drug interactions of NSAIDs with aspirin (see *Drug Interactions*).

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

DOMPERIDONE

Reportedly, electrophysiological *in vitro* and *in vivo* studies indicate an overall moderate risk of domperidone to prolong the QT interval in humans. In *in vitro* experiments on isolated cells transfected with hERG and on isolated guinea pig myocytes, exposure ratios ranged between 26- 47-fold, based on IC50 values inhibiting currents through IKr ion channels in comparison to the free plasma concentrations in humans after administration of the maximum daily dose of 10 mg administered 3 times a day. Safety margins for prolongation of action potential duration in *in vitro* experiments on isolated cardiac tissues exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 45-fold. Safety margins in *in vitro* pro-arrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 9- up to 45-fold. In *in vivo* models the no effect levels for QTc prolongation in dogs and induction of arrhythmias in a rabbit model sensitized for torsade de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by more than 22-fold and 435-fold, respectively. In the anesthetized guinea pig model following slow intravenous infusions, there were no effects on QTc at total plasma concentrations of 45.4 ng/mL, which are 3fold higher than the total plasma levels in humans at maximum daily dose (10 mg administered 3 times a day). The relevance of the latter study for humans following exposure to orally administered domperidone is uncertain.

In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 3-fold.

At a high, maternally toxic dose (more than 40 times the recommended human dose), teratogenic effects were seen in the rat. No teratogenicity was observed in mice and rabbits.

NAPROXEN

Carcinogenesis

Reportedly, a 2-year study was performed in rats to evaluate the carcinogenic potential of naproxen at rat doses of 8, 16, and 24 mg/kg/day (0.05, 0.1, and 0.16 times the maximum recommended human daily dose [MRHD] of 1500 mg/day based on a body surface area comparison). No evidence of tumorigenicity was found.

Mutagenesis

Naproxen tested positive in the in vivo sister chromatid exchange assay for but was not mutagenic in the in vitro bacterial reverse mutation assay (Ames test).

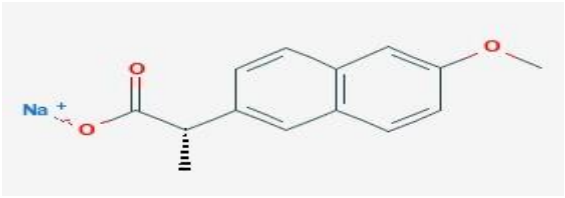
Impairment of Fertility

Male rats were treated with 2, 5, 10, and 20 mg/kg naproxen by oral gavage for 60 days prior to mating and female rats were treated with the same doses for 14 days prior to mating and for the first 7 days of pregnancy. There were no adverse effects on fertility noted (up to 0.13 times the MRDH based on body surface area).

7. Description

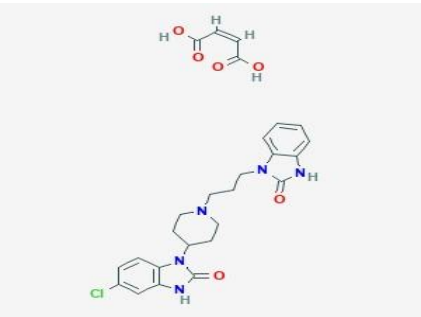
Naproxen Sodium

Naproxen Sodium is (2S)-2-(6-methoxynaphthalen-2-yl)propanoate Sodium with molecular formula of $C_{14}H_{13}NaO_3$ and having molecular weight 252.24 g/mol with the structural formula as below:



Domperidone Maleate

Domperidone Maleate is 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1yl)propyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one-maleate with molecular formula as $C_{22}H_{24}ClN_5O_2,C_4H_4O_4$ and molecular weight as 452g/mol with the structural formula as below:



DOMSTAL NP 250

Domperidone and Naproxen Sodium Tablets are brown coloured, circular, biconvex, both sides plain & film coated tablets. The excipients used are Lactose anhydrous, Microcrystalline cellulose, Starch, Maleic Acid, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Talcum. Magnesium Stearate, Colloidal Silicon dioxide, Sodium Starch Glycolate, Polyvinyl Alcohol, Glycerol Monostearate, Polysorbate 80, Triacetin, Modified Starch, Titanium Dioxide and Red Oxide of Iron.

DOMSTAL NP 500

Domperidone and Naproxen Sodium Tablets are brown coloured, caplet shaped, biconvex, both sides plain & film coated tablets. The excipients used are Lactose anhydrous, Microcrystalline cellulose, Starch, Maleic Acid, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Talcum. Magnesium Stearate, Colloidal Silicon dioxide, Sodium Starch Glycolate, Polyvinyl Alcohol, Glycerol Monostearate, Polysorbate 80, Triacetin, Modified Starch, Titanium Dioxide and Red Oxide of Iron.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

DOMSTAL NP is available in strip of 10 tablets.

8.4 Storage and handing instructions

- Store protected from light and moisture, at a temperature not exceeding 30°C.
- Keep all medicines out of reach of children.

9. Patient Counselling Information

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

9.6 Contents of the pack and other information

9.1 What DOMSTAL NP is and what it is used for

DOMSTAL NP is a fixed dose combination of two medicines named domperidone and naproxen. Domperidone belongs to a group of medicines called 'dopamine antagonists' and naproxen belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs), which are used to reduce inflammation and pain.

DOMSTAL NP is used for the treatment of migraine.

9.2 What you need to know before you use DOMSTAL NP

Do not take DOMSTAL NP if:

- you are allergic (hypersensitive) to domperidone, naproxen, naproxen sodium or aspirin, other NSAIDs or any other pain relief medicines (such as ibuprofen or diclofenac) or any of the other ingredients of DOMSTAL NP.

  Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- you have a tumour of the pituitary gland (prolactinoma)
- you have a blockage or tear in your intestines
- you have black, tarry bowel motions (stools) or notice blood in your bowel motions. This could be a sign of bleeding in the stomach or intestines or you have now or have ever had any problems with your stomach or gut (intestine) like an ulcer or bleeding or you have previously experienced bleeding or perforation in your stomach while taking NSAIDs.
- you have a moderate or severe liver disease.
- your ECG (electrocardiogram) shows a heart problem called "prolonged QT corrected interval".
- you have or had a problem where your heart cannot pump the blood round your body as well as it should (condition called heart failure).
- you have a problem that gives you a low level of potassium or magnesium, or a high level of potassium in your blood
- you are taking certain medicines (see *Other medicines and DOMSTAL NP*)
- you have severe problems with your kidneys
- you are in the last three months of pregnancy

Do not take DOMSTAL NP if any of the above applies to you. If you are not sure, talk to your doctor before taking DOMSTAL NP.

Warnings and precautions

Before taking this medicine contact your doctor if:

- you suffer from liver problems (liver function impairment or failure) (see *Do not take DOMSTAL NP if*)
- you suffer from kidney problems (kidney function impairment or failure). It is advisable to ask your doctor for advice in case of prolonged treatment as you may

need to take a lower dose or take this medicine less often, and your doctor may want to examine you regularly.
- you have asthma or allergies (like hayfever) or have had swelling of the face, lips, eyes or tongue in the past.
- you have a feeling of weakness (perhaps because of an illness) or you are an older person.
- you have lumps in your nose (polyps) or you sneeze a lot or have a runny, blocked, or itchy nose (rhinitis).
- you have problems with your kidneys or liver.
- you have problems with the way that your blood clots.
- you have problems with the blood vessels (arteries) anywhere in your body.
- you have too much fat (lipid) in your blood (hyperlipidaemia).
- you have an autoimmune condition, such as 'systemic lupus erythematosus' (SLE, causes joint pain, skin rashes and fever) and colitis or Crohn's disease (conditions causing inflammation of the bowel, bowel pain, diarrhoea, vomiting and weight loss).

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking DOMSTAL NP. Do this even if they have applied in the past.

If you have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker), you should discuss your treatment with your doctor or pharmacist. DOMSTAL NP may be associated with an increased risk of heart rhythm disorder and cardiac arrest. This risk may be more likely in those over 60 years old. The risk also increases when DOMSTAL NP is given together with some drugs. Tell your doctor or pharmacist if you are taking drugs to treat infection (fungal infections or bacterial infection) and/or if you have heart problems or AIDS/HIV (see *Other medicines and DOMSTAL NP*).

DOMSTAL NP should be used at the lowest effective dose in adults and adolescents 12 years of age and older and a body weight of 35kg or more.

While taking DOMSTAL NP, contact your doctor if you experience heart rhythm disorders such as palpitations, trouble breathing, loss of consciousness. Treatment with DOMSTAL NP should be stopped.

Other medicines and DOMSTAL NP

Please tell your doctor if you are taking or have recently taken any other medicines. This includes medicines you can buy without a prescription, including herbal medicines. This is because DOMSTAL NP can affect the way some other medicines work. Also, some medicines can affect the way DOMSTAL NP works.

Do not take DOMSTAL NP if you are taking medicine to treat:

- Fungal infections such as azole anti-fungals, specifically oral ketoconazole, fluconazole or voriconazole.
- Bacterial infections, specifically erythromycin, clarithromycin, telithromycin, moxifloxacin, pentamidine (these are antibiotics)
- Heart problems or high blood pressure (e.g., amiodarone, dronedarone, quinidine, disopyramide, dofetilide, sotalol, diltiazem, verapamil)

- Psychoses (e.g., haloperidol, pimozide, sertindole)
- Depression (e.g., citalopram, escitalopram)
- Gastro-intestinal disorders (e.g., cisapride, dolasetron, prucalopride)
- Allergy (e.g., mequitazine, mizolastine)
- Malaria (in particular halofantrine)
- AIDS/HIV (protease inhibitors)
- Cancer (e.g., toremifene, vandetanib, vincamine) Tell your doctor if you are taking:
- Other pain killers, like aspirin, ibuprofen, diclofenac and paracetamol.
- Medicine to stop your blood clotting, like warfarin, heparin or clopidogrel.
- A hydantoin (for epilepsy), like phenytoin.
- Sulfonamide medicines, like hydrochlorothiazide, acetazolamide, indapamide and including sulfonamide
- A sulfonylurea (for diabetes), like glimepiride or glipizide.
- An 'ACE inhibitor' or any other medicine for high blood pressure like cilazapril, enalapril or propranolol.
- An angiotensin-II receptor antagonist, like candesartan, eprosartan or losartan. A diuretic (water tablet) (for high blood pressure), like furosemide.
- A 'cardiac glycoside' (for heart problems), like digoxin.
- A steroid (for swelling and inflammation), like hydrocortisone, prednisolone and dexamethasone.
- Probenecid (for gout).
- Methotrexate (used to treat skin problems, arthritis or cancer).
- Ciclosporin or tacrolimus (for skin problems or after an organ transplant).
- Mifepristone (used to end pregnancy or to bring on labour if the baby has died). Aspirin/ acetylsalicylic acid to prevent blood clots.

Tell your doctor if you are taking drugs to treat infection, heart problems or AIDS/HIV.

<u>DOMSTAL NP and apomorphine</u>

Before you use DOMSTAL NP and apomorphine, your doctor will ensure that you tolerate both medicines when used simultaneously. Ask your doctor or specialist for a personalised advice.

It is important to ask your doctor if DOMSTAL NP is safe for you when you are taking any other medicines, including medicines obtained without prescription.

Pregnancy and breast-feeding

- Do not take DOMSTAL NP if you are in the last three months of pregnancy, as it can harm your baby.
- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or advice before taking this medicine. Small amounts of domperidone have been detected in breast-milk. DOMSTAL NP may cause unwanted side effects affecting the heart in a breast-fed baby. DOMSTAL NP should be used during breast feeding only if your physician considers this clearly necessary.
- Naproxen may make it more difficult to become pregnant. You should tell your doctor if you are planning to become pregnant or if you have problems becoming pregnant.

Driving and using machines:

DOMSTAL NP may make you tired, drowsy, dizzy, have problems with your eyesight and balance, depressed or have difficulty sleeping. Talk to your doctor if any of these happen to you and do not drive or use any tools or machines.

Important information about some of the ingredients of DOMSTAL NP

This medicine contains lactose. If you have been told that you cannot digest or tolerate some sugars, talk to your doctor before taking DOMSTAL NP.

9.3 How to use DOMSTAL NP

Medicines which contain naproxen may be associated (linked) with a small increased risk of heart attack ('myocardial infarction') or stroke. Any risk is more likely with higher doses and prolonged (longer term) treatment. **Do not exceed (take more than) the recommended dose or duration (length) of treatment**.

Always take DOMSTAL NP exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

For oral administration (by mouth)
Swallow the tablets whole with a little water.
While you are taking DOMSTAL NP, your doctor will want to see you to check you are on the right dose for you and look for any side effects. This is particularly important if you are elderly.

Older people and people with liver and kidney problems
Your doctor will decide your dose and may tell you to take the medicine less often.

If you take more DOMSTAL NP than you should
Contact your doctor, pharmacist or nearest hospital casualty department immediately if you have taken more tablets than you should. Take the medicine pack with you. This is so the doctors know what you have taken.

In the event of overdose, symptomatic treatment could be implemented. An ECG monitoring could be undertaken, because of the possibility of a heart problem called prolonged QT interval.

Symptoms of overdose are headache, feeling or being sick, heartburn, epigastric pain (upset stomach), diarrhoea, bleeding of the stomach or intestines, disorientation, temporary changes to liver functions, reducing the time it takes for your blood to clot, stopping breathing, body produces too much acid, unconsciousness, drowsiness, dizziness, ringing or buzzing in the ears, fainting, feeling sleepy, confused, uncontrolled movements (especially in children) which include unusual eye movements, unusual movements of the tongue or abnormal posture (such as a twisted neck).fits and excitation.

If you forget to take DOMSTAL NP

If you forget to take a dose, do not worry. Take it as soon as you remember, then carry on as before. If you do not take your medicine on one day, take your normal dose on the next day. Do not take a double dose to make up for a forgotten dose.

If you stop taking DOMSTAL NP
Talk to your doctor before you stop taking the tablets and follow their advice.

If you have any further questions on the use of this medicine, ask your doctor.

9.4 Possible Side Effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Medicines which contain naproxen may be associated with a small increased risk of heart attack ('myocardial infarction') or stroke.

Stop taking DOMSTAL NP and tell a doctor straight away if any of the following side effects happen. You may need urgent medical treatment:

Serious stomach or gut problems, signs include:

- Bleeding from the stomach, seen as vomit which has blood in it, or bits that look like coffee grounds.
- Bleeding from your back passage (anus), seen as passing black sticky bowel motions (stools) or bloody diarrhoea.
- Ulcers or holes forming in your stomach or gut sometimes fatal particularly in elderly. Signs include upset stomach, stomach pain, fever, feeling or being sick.
- Problems with your pancreas. Signs include severe stomach pain which spreads to your back.
- Worsening of ulcerative colitis or Crohn's disease, seen as pain, diarrhoea, vomiting and weight loss.

Allergic reactions, signs include:

- Sudden swelling of your throat, face, hands or feet.
- Difficulty breathing, tightness in your chest. Skin rashes, blisters or itching.

Severe skin rashes, signs include:

- A severe rash that develops quickly, with blisters or peeling of your skin and possibly blisters in your mouth, throat or eyes. Fever, headache, cough and aching body may happen at the same time.
- Blistering of skin when exposed to sunlight (porphyria cutanea tarda) seen most on arms face and hands.

Liver problems, signs include:

- Yellowing of your skin or the whites of your eyes (jaundice).
- Feeling tired, loss of appetite, feeling or being sick and pale coloured stools (hepatitis) and problems (including hepatitis), shown in blood tests.

Heart attack, signs include:

- Chest pain which may spread to your neck and shoulders and down your left arm.

Stroke, signs include:

- Muscle weakness and numbness. This may only be on one side of your body. A suddenly altered sense of smell, taste, hearing or vision, confusion.

Meningitis, signs include:

- Fever, feeling or being sick, a stiff neck, headache, depression, vertigo ,drowsiness, sensitivity to bright light and confusion (most likely in people with autoimmune conditions such as 'systemic lupus erythematosus').

- You notice any uncontrolled movements. These include irregular eye movements, unusual movements of the tongue, and abnormal posture such as a twisted neck, trembling and muscle stiffness. This is more likely to happen in children. These symptoms should stop once you stop taking DOMSTAL NP.
- You have a very fast or unusual heartbeat. This could be a sign of a life-threatening heart problem.
- You have a fit (seizure).

Other possible side effects:

Stomach and gut

- Heartburn
- indigestion
- gastritis (an inflammation of the lining of the stomach)
- dry mouth
- throat irritation
- decreased appetite
- stomach ache
- feeling sick or being sick
- constipation
- diarrhoea
- wind
- inflammation of the food pipe (oesophagus)

Side effects on the gut can be fatal, particularly in the elderly.

Blood

- a reduction in the number of platelets (thrombocytopenia)
- decreased platelet aggregation
- an increase or decrease in white blood cells
- a reduction of the quantity of the oxygen-carrying pigment haemoglobin in the blood (anaemia) caused by decreased production (aplasia) or increased destruction (haemolysis) of red blood cells
- high levels of potassium in the blood (hyperkalaemia) or inflammation of blood vessels (vasculitis).

Mental illness

- Having difficulty sleeping or changes in your patterns of dreaming.
- Depression.
- Confusion or seeing and possibly hearing things that are not there (hallucinations).

Nervous system

- Headache.
- Fits or seizures, feeling dizzy or light-headed or sleepy.
- Pins and needles or numbness of your hands and feet. Difficulty with your memory or concentration.

Eyes and ears

- Changes to your eyesight, eye pain.

- Changes to your hearing, including ringing in the ears (tinnitus) and hearing loss.
- Dizziness that causes problems with your balance.
- Abnormal eye movements

Heart and circulation

- Swelling of your hands, feet or legs (oedema), this may be with chest pains, tiredness, shortness of breath (cardiac failure).
- A fluttering feeling in your heart (palpitations), slow heart beat or high blood pressure.
- Problems with the way your heart pumps blood around the body or damage to your blood vessels. Signs may include tiredness, shortness of breath, feeling faint, general pain.

Chest

- Difficulty breathing, including shortness of breath, wheezing or coughing. Pneumonia or swelling of your lungs.

Skin and Hair

- Skin rashes including redness, hives, pimples and blisters on your body and face Bruising, itching, sweating, skin being more sensitive to the sun or hair loss.

Urinary

- Blood in your water (urine) or kidney problems
- Inability to urinate

Other

- Thirst, fever, feeling tired or generally unwell.
- A sore mouth or mouth ulcers.
- Muscle pain or weakness.
- Problems for women in getting pregnant.
- Breast enlargement in men
- In women, menstrual periods may be irregular or stop
- Lowering of sexual drive (libido) in men
- Feeling anxious
- 'Systemic lupus erythematosus' (SLE). Signs include fever, rash, problems with your kidneys and joint pain.

Side effects such as feeling drowsy, nervous, agitated or irritable or having a fit are more likely to happen in children.

Reporting of suspected adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
https://torrentpharma.com/index.php/site/info/adverse_event_reporting

By reporting side effects, you can help provide more information on the safety of this medicine

9.5 How to store DOMSTAL NP

- Store protected from light and moisture, at a temperature not exceeding 30°C.
- Keep all medicines out of the reach of children

9.6 Contents of the pack and other information

What DOMSTAL NP contains:

The active substances are domperidone and naproxen.

DOMSTAL NP 250

The excipients used are Lactose anhydrous, Microcrystalline cellulose, Starch, Maleic Acid, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Talcum. Magnesium Stearate, Colloidal Silicon dioxide, Sodium Starch Glycolate, Polyvinyl Alcohol, Glycerol Monostearate, Polysorbate 80, Triacetin, Modified Starch, Titanium Dioxide and Red Oxide of Iron.

DOMSTAL NP 500

The excipients used are Lactose anhydrous, Microcrystalline cellulose, Starch, Maleic Acid, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Talcum. Magnesium Stearate, Colloidal Silicon dioxide, Sodium Starch Glycolate, Polyvinyl Alcohol, Glycerol Monostearate, Polysorbate 80, Triacetin, Modified Starch, Titanium Dioxide and Red Oxide of Iron.

What DOMSTAL NP looks like DOMSTAL NP 250

Domperidone and Naproxen Sodium Tablets are brown coloured, circular, biconvex, both sides plain & film coated tablets.

DOMSTAL NP 500

Domperidone and Naproxen Sodium Tablets are brown coloured, caplet shaped, biconvex, both sides plain & film coated tablets

Pack Sizes:

DOMSTAL NP is available in strip of 10 tablets.

10. Details of manufacturer

Manufactured by:

Akums Drugs & Pharmaceuticals Ltd.

19, 20, 21, Sector-6A, I.I.E., SIDCUL, Ranipur, Haridwar – 249403, Uttarakhand.

11. Details of permission or licence number with date

Mfg Licence No.: 10/UA/2004 issued on 23.11.2019

12. Date of revision

FEB-2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/DOMSTAL NP 250, 500/FEB-2022/02/PI