Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Relifex 500 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of nabumetone.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.
Dark red, film-coated, tablets marked "Relifex" on one side and "500" on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the symptomatic management of various arthritides, such as rheumatoid arthritis, osteoarthritis, spondylitis, gout, and of acute musculoskeletal disorders.

4.2 Posology and method of administration

Route of Administration

Oral.

Recommended Dosage

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms *(see section 4.4)*.

Adults:

The recommended daily dose is two tablets (1 g) taken as a single night time dose with or without food. For severe or persistent symptoms, or during acute exacerbations, an additional one or two tablets (500 mg to 1 g) may be given as a morning dose.

Older patients:

Total daily dosage should not exceed 1 g. An initial dose of 500 mg should be used. Blood levels may be higher. NSAIDs should be used with particular caution in older patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed. See also 4.4.

Children:

There are no clinical data to enable a dosage recommendation to be made for children.

Where appropriate for acute conditions, including sports injuries two tablets (1g) may be given as a loading dose. Total dosage should not exceed 2 g a day.

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

4.3 Contraindications

- Use in patients with active or history of recurrent, peptic ulcer /haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- In patients who have experienced asthma, urticaria or allergic type reactions after taking acetylsalicylic acid or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients
- In patients with severe hepatic and renal failure
- In patients with a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- In the third trimester of pregnancy and in nursing mothers
- Use in patients with a history of hypersensitivity (e.g. bronchospasm, rhinitis, urticaria) to nabumetone or the excipients (see section 6.1)
- In patients with severe heart failure, and in patients with current cerebrovascular or other haemorrhage

4.4 Special warnings and precautions for use

The use of nabumetone with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

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

Gastrointestinal bleeding, Ulceration and Perforation:

Gastrointestinal bleeding, ulceration or perforation, which may be fatal, has been reported with all NSAIDs, and may occur at any time during treatment, with or without symptoms or a previous history of serious gastrointestinal events. The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAIDs doses, in patients with a history of ulcers, particularly if complicated with haemorrhage or perforation *(see section 4.3, contraindications)*, and in older patients

These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk *(see below and section 4.5, Interactions)*.

Patients with a history of gastrointestinal toxicity, particularly when older, should be alerted to report any unusual abdominal symptoms indicative for ulceration (especially gastrointestinal bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, NSAIDs, SSRIs or anti-platelet agents such as acetylsalicylic acid and clopidogrel *(see section 4.5, Interactions)*.

When gastrointestinal bleeding or ulceration occurs in patients receiving nabumetone, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated *(see section 4.8, Undesirable effects)*.

In a review of both pre- and post-registration data from clinical trials with nabumetone, the mean cumulative frequencies of GI perforations, ulcers or bleeds (PUBs) in patients treated from 3 to 6 months, 1 year and 2 years were respectively 0.3%, 0.5% and 0.8%. Although these figures seem low, the prescribing physician should be aware that these ADR can occur even in the absence of previous peptic disease.

Older patients
Older patients have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal (*see section 4.2, Posology and method of administration*). Prolonged use of NSAIDs in older patients is not recommended. Where prolonged therapy is required, patients should be reviewed regularly. It is possible that the recommended dosage regimen may require further modification in the presence of severe renal dysfunction.

Children
The safety of the drug in children has not been demonstrated and its use cannot therefore be recommended in this group.

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

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for nabumetone.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with nabumetone after careful consideration.

Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Impaired female fertility:
The use of nabumetone may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of nabumetone should be considered.

Serious Skin Reactions:
Serious skin reaction, including exfoliative dermatitis, Steven-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported rarely in association with the use of NSAIDs, including nabumetone (see section 4.8).

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, nabumetone should be withdrawn immediately and an alternative treatment considered (as appropriate).

Patients appear to be at the highest risk of these reactions occurring in the majority of cases within the first two months of treatment. Nabumetone should be discontinued at the first appearance of skin rash, mucosal lesions, or any sign of hypersensitivity.

If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of nabumetone, treatment with nabumetone must not be restarted in this patient at any time.

Others
NSAIDs may mask the signs or symptoms of an infection (fever, pain and swelling).

Cases of blurred vision or reduced visual activity have been reported with NSAID use, including nabumetone. Patients presenting with these events must be submitted to ophthalmological examination.

Caution should be used when administering nabumetone to patients with:
Previous acetylsalicylic acid- or other NSAID-induced asthma, urticaria or other allergic type reactions. Since fatal asthma attacks have been reported in such patients receiving other NSAIDs, the first administration of nabumetone should be medically supervised.
SLE and mixed connective tissue disease: In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders, there may be an increased risk of aseptic meningitis (see section 4.8).
Severe hepatic impairment. As with other NSAIDs, abnormalities of liver function tests, rare cases of jaundice and hepatic failure (some of them with fatal outcomes), have been reported. A patient with signs/symptoms suggesting liver dysfunction or who has experienced an abnormal liver function test while on nabumetone therapy should be evaluated for evidence of development of a more serious hepatic reaction. Nabumetone should be discontinued if such a reaction occurs.

Severe renal impairment (creatinine clearance less than 30 ml/min): laboratory tests should be performed at baseline and within some weeks of starting therapy. Further tests should be carried out as necessary; if the impairment worsens, discontinuation of therapy may be warranted. In moderate renal impairment (creatinine clearance 30 to 49 ml/min) there is a 50% increase in unbound plasma 6-MNA and dose reduction may be warranted (see section 4.5).

Relifex contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies between nabumetone and the above have been performed.

Caution is therefore recommended for concomitant therapy with the drugs listed below.

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants *(see section 4.4)*; its concomitant administration with nabumetone should be undertaken with caution and overdose signals carefully monitored.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Ciclosporin: NSAIDs increase the risk of nephrotoxicity with this medicinal product.

Other NSAIDs: use of more than one NSAID is not recommended.
In general, NSAIDs interact with the following medicinal products, by increasing their concentrations:
- cardiac glycosides
- methotrexate
- lithium

Hyperkalaemia might develop, particularly with concomitant potassium-sparing diuretics administration.

Diuretics and other antihypertensives drugs such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor antagonists (ARA) may present with decreased effect when concomitantly administered with NSAID; in some persons (such as elderly or dehydrated patients) this could lead to a further decrease in renal function and eventually to acute renal failure (ARF). Consequently, hydration and frequent monitoring of these patients is warranted.

Concomitant administration of nabumetone with other highly protein-bound drugs, e.g. sulphonamides, sulphonylureas or hydantoin should be undertaken with caution and overdose signals carefully monitored.

Oral hypoglycemic agents: inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

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

Probenecid: Reduction in the metabolism of nabumetone and a reduction in the elimination of nabumetone and metabolites.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding *(see section 4.4)*.

Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycosides and increased plasma concentrations.

Quinolone antibiotics: Animal data indicate that NSAIDs increase the risk of convulsions associated with quinolone antibiotics. Patients taking nabumetone and quinolones may have an increased risk of developing convulsions.

Tacrolimus: Possibly increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
Zidovudine: Increased risk of haemotogical when NDSAIs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HOV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Alcohol, bisphosphonates, oxpentifylline (pentoxyfilline) and sulfinpyrazone: May potentiate the GI side-effects and the risk of bleeding or ulceration.

The following commonly available drugs do not affect nabumetone metabolism and bioavailability: paracetamol, cimetidine, aluminium hydroxide antacids.

The absorption of Relifex is not impaired by food.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no clinical trial experience with the use of nabumetone during human pregnancy.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. From the 20th week of pregnancy onward, nabumetone use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, nabumetone should not be given unless clearly necessary. If nabumetone is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to nabumetone for several days from gestational week 20 onward. Nabumetone should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

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

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, nabumetone is contraindicated during the third trimester of pregnancy (see sections 4.3).

Breast-feeding
There is no clinical trial experience with the use of nabumetone during lactation. It is not known whether nabumetone is excreted in human milk; however, 6-MNA is excreted in the milk of lactating rats. With the potential for serious adverse reactions in breast fed infants from nabumetone, a decision should be made whether to discontinue breast-feeding or to discontinue the drug, taking into account the importance of the drug to the mother.

Fertility
See section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

Dizziness and confusion have been reported after administration of nabumetone. If these symptoms occur, the patient must not drive or operate machinery.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo and comparator groups has not been taken into account in estimation of these frequencies. Rare and very rare events were generally determined from spontaneous data.

Blood and lymphatic system disorders
Very rare: Thrombocytopenia
Not known: Anaemia (incl. aplastic anaemia and haemolytic anaemia)

Immune system disorders
Very rare: Anaphylaxis, anaphylactoid reaction

Psychiatric disorders
Uncommon: Confusion, nervousness, insomnia
Not known: Hallucinations

Nervous system disorders
Uncommon: Somnolence, dizziness, headache, paraesthesia
Not known: Aseptic meningitis (especially in patients with existing autoimmune disorders such as systemic lupus erythematosus, mixed connective tissue disease, with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4)

Eye disorders
Uncommon: Abnormal vision, eye disorder

Ear and labyrinth disorders
Common: Tinnitus, ear disorder

Vascular disorders
Common: Increases in blood pressure

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, respiratory disorder, epistaxis
Very rare: Interstitial pneumonitis

Gastrointestinal disorders
Common: Diarrhoea, constipation, dyspepsia, gastritis, nausea, abdominal pain, flatulence
Uncommon: Duodenal ulcer, GI bleeding, gastric ulcer, GI disorder, melena, vomiting, stomatitis, dry mouth
Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, many occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

Hepatobiliary disorders
Very rare: Hepatic failure, jaundice

Skin and subcutaneous tissue disorders
Common: Rash, pruritus
Uncommon: Photosensitivity, urticaria, sweating
Very rare: Bullous reactions including toxic epidermal necrolysis, Stevens Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, erythema multiforme, angioedema, pseudoporphyria, alopecia

Musculoskeletal and connective tissue disorders
Uncommon: Myopathy

Renal and urinary disorders
Uncommon: Urinary tract disorder
Very rare: Renal failure, nephrotic syndrome

Reproductive system and breast disorders
Very rare: Menorrhagia

General disorders and administration site conditions
Common: Oedema
Uncommon: Asthenia, fatigue

Investigations
Uncommon: Elevate liver function tests

Summary of safety profile
Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with nabumetone treatment (see section 4.4).

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms and signs

There is no information about overdose.

Symptoms include nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness and occasionally convulsions. In cases of significant poisoning, acute renal failure and liver damage are possible.

Treatment

There is no specific antidote and the active metabolite 6-MNA is not dialysable. Accidental overdose should be treated with gastric lavage followed by activated charcoal and appropriate supportive therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other anti-inflammatory and antiheumatic agents, non-steroids, ATC code: M01 AX01.

Relifex contains as active substance 4-(6'-methoxy-2'naphthyl)-2-butanone with the generic name nabumetone. Nabumetone is an anti-inflammatory agent of a non-acid, non-steroidal nature with anti-inflammatory, analgesic and antipyretic effects. The anti-inflammatory effect is assumed to be due to the ability to inhibit prostaglandin syntheses. Nabumetone has a weak effect on platelet aggregation caused by collagen and no effect on bleeding time. Lower frequency of peptic ulcers, bleeding or perforation has been reported in comparison with other NSAIDS.

Nabumetone is a pro-drug of the active metabolite 6-methoxy-2-napthylacetic acid (6-MNA). The effect of Relifex is obtained from the metabolite 6-MNA.

5.2 Pharmacokinetic properties

Nabumetone is absorbed almost entirely (>80%) from the gastrointestinal tract, but the first-pass metabolism is extensive, and no unchanged nabumetone is found in the plasma. The absorption rate is increased by concurrent ingestion of food or milk. However, the total quantity of the active metabolite in plasma is unchanged. In-vivo studies suggest that 6-MNA does not undergo any enterohepatic circulation. The bioavailability of 6-MNA in administration of Relifex is approximately 35% (23-52%). The maximum plasma level of 6-MNA is reached at around 3 (1-12) hours after dosing. 6-MNA binds strongly to plasma proteins (>99%). The free fraction is dependent on the total concentration of 6-MNA and is proportional to dose in the range

1-2 g. The free fraction is 0.2-0.3% for 1 g daily dosing and approximately 0.6-0.8% with 2 g daily dosing. Because of its strong binding to proteins, 6-MNA cannot be dialysed.
Following intravenous administration, the distribution volume has been measured as 7.5 (6.8-8.4) l and clearance as 4.4 (1.0-6.9) ml/min.
The half-life at steady-state following an oral dose of 1 g is 22.5±3.7 hours.
Nabumetone is metabolised to 6-MNA. 6-MNA distributes into inflamed tissue and crosses the placenta into foetal tissue. It is found in the milk of lactating females. 6-MNA is eliminated by metabolism, principally by conjugation with glucuronic acid, and odemethylation followed by conjugation, the main route of excretion being the urine.

Older people:
The steady-state plasma concentration in older people is usually higher and the half-life longer (29.8±8.1 hours) than in young healthy individuals, but the different intervals overlap to a great extent.

Renal impairment:
In patients with severely impaired renal function (creatinine clearance <30 ml/min), the mean value of the half-life of 6-MNA increased to around 40 hours and the plasma levels are 30% higher than in other patients. In patients who underwent dialysis, the steady-state plasma concentration of the active metabolite was equivalent to the values observed in healthy individuals.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium starch glycolate Type A
Sodium lauryl sulphate
Hypromellose (E464)
Magnesium stearate (E572)
Microcrystalline cellulose (E460)
Saccharin sodium
Liquid caramel flavour (E150a)
Carmine (E120)
Iron oxide yellow (E172)
Titanium dioxide (E171)
Talc
Macrogol 400
Carnauba wax (E903)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container

Opaque high density polythene bottles with white, opaque high density polyethylene caps in packs of 56 tablets. Blister packs in packs of 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
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8 MARKETING AUTHORISATION NUMBER

PA23355/039/001

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