Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Relifex 500 mg / 5 ml oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of suspension contains 500 mg nabumetone.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension.
White to off-white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the symptomatic management of various arthritides, such as rheumatoid arthritis, osteoarthritis, spondylitis, gout, etc., 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 10 ml (1g) taken as a single night time dose. For severe or persistent symptoms, or during acute exacerbations, an additional 5 ml or 10 ml (500 mg to 1g) may be given as a morning dose.

Elderly: Total daily dosage should not exceed 1g.

Non-steroidal anti-inflammatory drugs should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed. *(See also section 4.4).*

Prolonged use of non-steroidal anti-inflammatory drugs is not recommended in the elderly. However, where prolonged treatment proves necessary, patients should be reviewed regularly.

Children: There are no clinical data to recommend use of ‘Relifex’ in children.

Where appropriate for acute conditions, including sports injuries, 10ml (1g) may be given as a loading dose. Total dosage should not exceed 2g a day.

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

4.3 Contraindications

1. Use in patients with active or history of peptic or gastrointestinal ulceration or haemorrhage(two or more distinct episodes of proven ulceration or bleeding).
2. Use in patients with a history of gastrointestinal bleeding or perforation related to previous NSAID therapy.
3. Use in patients hypersensitive (e.g. bronchospasm, rhinitis, urticaria) to the active ingredients, the excipients or to other non steroidal anti-inflammatory drugs.
4. Severe heart failure.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms *(see section 4.2, and gastrointestinal and cardiovascular risks below).*

Gastrointestinal bleeding, Ulceration and Perforation:
Gastrointestinal bleeding, ulceration or perforation, which may be fatal, has been reported with all non-steroidal anti-inflammatory drugs, 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 non-steroidal anti-inflammatory doses, in patients with a history of ulcers, particularly if complicated with haemorrhage or perforation *(see section 4.3),* and in the elderly. 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).*

Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the early stages of treatment.

If gastrointestinal bleeding or ulceration occurs in patients receiving Relifex the treatment should be withdrawn.

Non-steroidal anti-inflammatory drugs 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).*

In patients with renal, cardiac or hepatic impairment, caution is required since the use of non-steroidal anti-inflammatory drugs may result in deterioration of renal function. Assessment of renal function should occur prior to the initiation of therapy and regularly thereafter.

Elderly
The elderly have an increased frequency of adverse reactions to non-steroidal anti-inflammatory drugs, especially gastrointestinal bleeding and perforation which may be fatal *(see section 4.2).*

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).

Female fertility:
The use of non-steroidal anti-inflammatory drugs, such as nabumetone, may impair female fertility, and is not recommended in women attempting to conceive. In women who have difficulty conceiving or who are undergoing investigation of infertility, withdrawal of nabumetone should be considered.

Serious Skin Reactions:
Serious skin reaction, some of them fatal, including exfoliative dermatitis, Steven-Johnson Syndrome, and Toxic Epidermal Necrolysis, have been reported very rarely in association with the use of non-steroidal anti-inflammatory drugs *(see section 4.8).* Patients appear to be at the highest risk of these reactions occurring in the majority of cases within the first month of treatment. Relifex should be discontinued at the first appearance of skin rash, mucosal lesions, or any sign of hypersensitivity.

Concomitant use of Non-steroidal Anti-inflammatory Drugs:
The use of Relifex with concomitant non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 selective inhibitors should be avoided.

As non-steroidal anti-inflammatory drugs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Suspension contains sodium benzoate.

4.5 Interaction with other medicinal products and other forms of interaction

Care should be taken in patients treated with any of the following drugs as interactions have been reported:

Anti-coagulants: anticoagulants	Non-steroidal anti-inflammatory drugs may enhance the effects of anti-coagulants *(see section 4.4).* Therefore, caution is prescribed when combining non-steroidal anti-inflammatory drugs and and a recurrent monitoring of these patients is advised.
Anti-platelet agents:	Aspirin and other anti-platelet agents may result in increased risk of gastrointestinal bleeding *(see section 4.4).*
Anti-hypertensives:	reduced anti-hypertensive effect.
Diuretics:	reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of non-steroidal anti-inflammatory drugs.
Cardiac glycosides:	NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.
Lithium:	decreased elimination of lithium.
Methotrexate:	decreased elimination of methotrexate
Ciclosporin:	increased risk of nephrotoxicity with non-steroidal anti-inflammatory drugs.
Other	non-steroidal anti-inflammatory drugs: avoid concomitant use of two or more non-steroidal anti-inflammatory drugs.
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.

Probenicid: reduction in metabolism and elimination of non-steroidal anti-inflammatory drugs and metabolites.

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

Selective serotonin re-uptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding *(see section 4.4).*

The absorption of 'Relifex' is not impaired by food.

4.6 Pregnancy and lactation

Nabumetone should not be used in pregnancy unless considered essential by the physician. There is no evidence of teratogenic effect in animal studies. The drug appears in the milk during lactation in rats.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Gastrointestinal disorders
The most commonly observed events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly may occur *(see section 4.4).*

Nausea (common), vomiting, diarrhoea, flatulence, constipation (uncommon), dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, dry mouth, exacerbation of colitis and Crohn's disease *(see section 4.4-special warnings and precautions for use)* have been reported following administration. Less frequently gastritis has been observed.

Cardiovascular disorders
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).*

Skin and subcutaneous tissue disorders
Bullous reactions including Steven-Johnson Syndrome and Toxic Epidermal Necrolysis (very rare).

Headache, dizziness, confusion, sedation, hypersensitivity, anaphylaxis, anaphylactoid reaction and angioedema have also been reported.

Hepatic side-effects of elevated liver function tests, jaundice and hepatic failure have occurred.

Thrombocytopenia has also been reported very rarely. There have been rare reports of renal side effects including interstitial nephritis, nephritic syndrome and renal failure.

4.9 Overdose

There is no specific antidote. Treatment is with gastric lavage followed by activated charcoal using up to 60g orally in divided doses, with appropriate supportive therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: M01A X

'Relifex' is a non-steroidal anti-inflammatory agent, which as presented to the gut is non-acidic and a minimal inhibitor of prostaglandin synthetase; thus it has a low propensity to cause irritation and damage to the gastric mucosa and improved gastric tolerance has been demonstrated. After absorption, 'Relifex' undergoes extensive metabolism in the liver. The major active metabolite is a potent inhibitor or prostaglandin synthetase and is responsible for the excellent anti-inflammatory activity demonstrated in clinical trials with 'Relifex'.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methylcellulose
Xanthan Gum
Sorbitol
Sodium Benzoate (E211)
Liquid vanilla flavour
Liquid buttermint flavour
Ammonium Glycyrrhizate
Glycerol
Dilute Hydrochloric Acid
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

White, opaque high density polythene bottles with wadless polypropylene caps. Pack sizes of 40ml (sample packs) and 300 ml.

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

Meda Health Sales Ireland Limited,
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Dunboyne,
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8 MARKETING AUTHORISATION NUMBER

PA 1332/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 17 December 2005

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