Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Religer 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg nabumetone.

Each film coated tablet also contains E110 and E122.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Pink/Red capsule shaped film-coated tablet, debossed 'NB500' on one side and 'G' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of osteoarthritis and rheumatoid arthritis requiring anti – inflammatory and analgesic treatment.

4.2 Posology and method of administration

For oral administration.

Adults:
The recommended daily dose is two tablets (1g) taken as a single dose at bedtime.

For severe or persistent symptoms, or during acute exacerbations, an additional 500mg-1g may be given as a morning dose.

Elderly:
Total daily dosage should not exceed 1 g. An initial dose of 500 mg should be used. Blood levels may be higher in elderly people, therefore non steroidal anti-inflamatory drugs (NSAIDs) should be used with particular caution in this group as elderly patients are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed. (see Section 4.4 Special warnings and precautions for use).

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

Children:
There are no clinical data to recommend use of nabumetone in children.

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

4.3 Contraindications

Hypersensitivity to nabumetone or to any other constituents of Religer Tablets 500mg.

Nabumetone should not be administered to patients with a history of, or active, peptic ulceration.

History of upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Nabumetone is contraindicated in patients who have previously shown hypersensitivity reactions such as asthma, rhinitis or urticaria in response to ibuprofen, aspirin, or other non–steroidal anti–inflammatory drugs.

Nabumetone is contraindicated in patients with severe hepatic impairment e.g. cirrhosis, and in patients with severe cardiac and renal failure (creatinine clearance < 30 ml/min). See section 4.4 – Special warnings and precautions for use.

During the last trimester of pregnancy (See section 4.6 Fertility, pregnancy and lactation).

Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors (See section 4.5 Interaction with other medicinal products and other forms of interaction).

Severe heart failure.

4.4 Special warnings and precautions for use

In all patients:
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 and GI and cardiovascular risks below). Patients on long term treatment should be reviewed at regular intervals. Nabumetone should be discontinued if no clinical benefit is seen or risk-benefit is no longer favourable.

Elderly:
The elderly are at increased risk of the serious consequences of adverse reactions, especially gastrointestinal bleeding and perforation which may be fatal (See section 4.2 Posology and method of administration). If an NSAID is considered necessary, the lowest effective dose should be used and the patient should be monitored for gastrointestinal bleeding.

Respiratory disorders:
Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Cardiovascular, renal and hepatic impairment:
The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (See also section 4.3 contraindications).

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 is 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).

Gastrointestinal bleeding, ulceration and perforation:
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with our without warning symptoms or a previous history of serious GI events.

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

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin or anti-platelet agents such as aspirin (see section 4.5 Interactions with other medicinal products and other forms of interaction).

When GI 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).

Intracranial haemorrhage:
As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.

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).

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.

Allergic type reactions:
The excipients E110 and E122 can cause allergic type reactions including asthma. Patients who are allergic to aspirin are more susceptible.

If a patient reports loss of vision or blurred vision, an eye examination should be performed.

4.5 Interaction with other medicinal products and other forms of interaction

Nabumetone has been shown to interact with the pharmacokinetic and pharmacodynamic characteristics of a number of drugs leading to potential adverse effects. Care should be taken in patients treated with any of the following:

Anti–hypertensive drugs: The anti-hypertensive effect of treatment is antagonised by NSAIDs.

Diuretics: NSAIDs are known to reduce the diuretic effect of these drugs and concomitant diuretic therapy can increase the risk of nephrotoxicity associated with NSAIDs. There is a possible risk of hyperkalaemia when potassium sparing diuretics are used concomitantly with nabumetone.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Lithium: Decreased elimination of lithium occurs when NSAIDs are co-administered and lithium toxicity may be precipitated.

Methotrexate: A number of NSAIDs have been shown to increase plasma levels of methotrexate (associated with decreased renal elimination of methotrexate and possibly competition for plasma protein binding sites) and so may induce methotrexate toxicity.

Ciclosporin: NSAIDs increase the risk of nephrotoxicity with this drug.

Aminoglycosides: Concomitant administration of aminoglycosides may lead to a reduction in renal function in susceptible individuals, decreased elimination of aminoglycosides and increased plasma concentrations in susceptible individuals.

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

Other analgesics: avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.3 Contraindications).

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

Corticosteroids: There is increased risk of gastrointestinal bleeding when corticosteroids are taken with NSAIDs (see section 4.4 Special warnings and precautions for use).

Anticoagulants: NSAIDs enhance the effect of anticoagulant drugs with increased risk of bleeding. Concomitant use of warfarin or heparin is not advised unless under direct medical supervision (see section 4.4 Special warnings and precautions for use).

Oral hypoglycaemic agents: Inhibition of metabolism of sulfonylurea drugs, prolonged half life and increased risk of hypoglycaemia.

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.

Anti-depressant drugs: Selective serotonin re–uptake inhibitors (SSRIs) have been shown to be associated with an increased risk of bleeding which is greater when NSAIDs are co-prescribed.

As the major circulating metabolite of nabumetone is highly plasma bound, patients receiving hydantoin anti-convulsants, oral anticoagulants and sulfonylureas should be monitored for signs of overdose. Dosages should be adjusted if necessary.

4.6 Fertility, pregnancy and lactation

Nabumetone is not recommended and should be avoided during pregnancy or in mothers who are breast feeding.

Pregnancy:
Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3 Contraindications). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Lactation:
In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Gastrointestinal: The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4 – Special warnings and precautions for use). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, dry mouth, faecal occult blood, ulcerative stomatitis, gastrointestinal haemorrhage, 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.

Hypersensitivity: Hypersensitivity reactions have been reported following treatment with NSAIDs including nabumetone. These may consist of (a) non–specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) various skin disorders, including rashes of various types, pruritis, urticaria, purpura, angioedema and, less commonly, bullous dermatoses (including epidermal necrolysis, erythema multiforme and exfoliative dermatitis).

Cardiovascular: 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 Special warnings and precautions for use).

Other adverse events reported less commonly include:

Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

Hepatic: Abnormal liver function, hepatitis and jaundice.

Neurological and special senses: Visual disturbance, optic neuritis, headaches, paraesthesia, reports of aseptic meningitis (especially in patients with existing auto-immune 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, Special warnings and precautions for use), depression, sedation, insomnia, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness.

Haematological: Thrombocytopenia, neutropenia, agranulocytosis, leucopenia, menorrhagia, aplastic anaemia and haemolytic anaemia.

Dermatological: Photosensitivity, alopecia and Stevens Johnson Syndrome.

4.9 Overdose

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

b) Therapeutic measure
Patients should be treated symptomatically as required.
Within one hour of ingestion of a potentially toxic amount, activated charcoal up to 60g orally in divided doses should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.
Good urine output should be ensured.
Renal and liver function should be closely monitored.
Patients should be observed for at least four hours after ingestion of potentially toxic amounts.
Frequent or prolonged convulsions should be treated with intravenous diazepam.
Other measures may be indicated by the patient's clinical condition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Nabumetone is a non-acidic non-steroidal anti-inflammatory agent which is a relatively weak inhibitor of prostaglandin synthesis. Following absorption from the gastrointestinal tract nabumetone is rapidly metabolised in the liver to the principal active metabolite, 6-methoxy-2-naphthylacetic acid (6-MNA) a potent inhibitor of prostaglandin synthesis.

5.2 Pharmacokinetic properties

Intravenous studies in rats with nabumetone indicate it to be rapidly distributed throughout the body, in keeping with its highly lipophilic character. The active metabolite, 6-MNA, binds strongly to plasma proteins; it is distributed 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 conjugation with glucuronic acid, and O-demethylation followed by conjugation, the main route of excretion being the urine. The plasma elimination half-life is about one day in man. When administered with food or milk, there is more rapid absorption; however, the total amount of 6–MNA in the plasma is unchanged.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber, which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose Microcrystalline
Sodium Laurilsulfate
Saccharin Sodium
Hypromellose
Sodium Starch Glycollate (Type A)
Magnesium Stearate
Titanium Dioxide (E171)
Carmoisine Aluminium Lake (E122)
Sunset Yellow Aluminium Lake (E110)
Macrogol 400
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25ºC. Keep the bottle and blister strips in the outer carton in order to protect from light.

6.5 Nature and contents of container

Cartons containing PVdC coated PVC blister strips with aluminium foil lidding and polypropylene container with tamper-evident polyethylene closure.

Available in packs of 10, 14, 20, 28, 30, 50, 56, 60, 100, 112, 168 and 250.
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

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