SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nabumetone Tablets 500mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg Nabumetone.

Excipient with known effect
Contains Carmoisine aluminium lake (E122).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Maroon, oval, biconvex, film-coated tablets impressed “C” on one face and the identifying letters “NB” on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nabumetone Tablets are indicated for use in osteoarthritis and rheumatoid arthritis requiring anti-inflammatory and analgesic treatment.

4.2 Posology and method of administration

Posology

Adults: The usual starting dose is 1g (two tablets) per day taken as a single daily dose at bedtime.
For severe or persistent symptoms, or during acute exacerbations an additional 500mg- 1g may be given as a morning dose.

Elderly: Blood levels may be higher in elderly patients because of accumulation of the drug as a result of reduced metabolism and elimination by the liver and kidneys. The recommended daily dose of 1g should not be exceeded in this age group and in some cases 500mg may give satisfactory relief. The risk of serious consequences of adverse effects is increased in the elderly. The lowest dose possible should be used and patients should be monitored for gastrointestinal bleeding for 4 weeks following initiation of therapy with nabumetone.
Children: Not recommended as there is no clinical data.

Method of Administration

For oral administration. Nabumetone should be administered with or after food to minimise the risk of gastrointestinal adverse effects.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Nabumetone must not be given to patients who have experienced asthma, urticaria, or allergictype reactions after taking acetylsalicylic acid or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.
- Nabumetone is contraindicated in patients with severe hepatic failure.
- Nabumetone is contraindicated in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Nabumetone is contraindicated in patients with active, or history of recurrent, peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Nabumetone is contraindicated in the third trimester of pregnancy and in nursing mothers.
- Nabumetone is contraindicated 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 minimum effective dose for the shortest duration necessary to control symptoms.

Elderly

Elderly have an increased frequency of adverse reactions to NSAIDs; especially gastrointestinal bleeding and perforation, which may be fatal (see section 4.2).

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 or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, 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 acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

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

Caution should be used 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).

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 gastro-intestinal disease (ulcerative colitis, Crohn's disease), as their condition may be exacerbated (see section 4.8).

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.

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 (e.g. 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).

Skin reactions
Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), 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 highest risk of these reactions early in the course of therapy, the onset of the reaction 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 other 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.

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.

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).

Excipients
Nabumetone contains carmoisine aluminium lake (E122), which may cause allergic reactions.

Nabumetone contains less than 1 mmol sodium (23 mg) per tablet, 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 above.
Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anticoagulation: NSAIDS may enhance the effects of anticoagulants, such as warfarin and other anticoagulants (see section4.4); 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).
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. sulfonamides, sulfonylureas or hydantoin should be undertaken with caution and overdose signals carefully monitored.

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

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.

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.

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.

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 (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 and 5.3).

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

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).

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 ulce 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:	Elevated liver function tests

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

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 the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 antirheumatic agents, non-steroids.
ATC code M01A X01.

Nabumetone is a non-acidic NSAID 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-naphylacetic acid (6-MNA) a potent inhibitor of prostaglandin synthesis. Nabumetone is a naproxen derivative and 6-MNA is structurally similar to naproxen.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of nabumetone are summarised in the table below:

Oral absorption (%)	≈ 80%
Presystemic metabolism to 6-MNA	≈ 100%
Normal half life of active metabolite (h) range mean	 16-27 hours 22 hours
Volume of distribution of 6-MNA (l)	7.5 $l.kg^{-1}$
Plasma protein binding of 6-MNA	≈ 99%

Absorption
Although nabumetone is absorbed essentially intact through the small intestine, extensive metabolism occurs during the first pass through the liver. As a result, concentrations in plasma of nabumetone are barely detectable after oral dosage.

Distribution
Intravenous studies in rats with nabumetone indicate it to be rapidly distributed throughout the body, in keeping with its highly lipophilic character.

Biotransformation and elimination
The active metabolite, 6-MNA, blinds 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 mean plasma elimination half life of 6-MNA is about 22 hours in man.

5.3 Preclinical safety data

No mutagenic activity was demonstrated in the Ames test or the mouse micronucleus test *in vivo*. However, chromosomal aberrations occurred in lymphocytes exposed *in vitro* to nabumetone or its active metabolite 6-MNA

at concentrations of 80µg/ml or higher. Nabumetone produced no carcinogenic effects in rats or mice in life time studies.
No teratogenic potential has been demonstrated in experiments with animals. High doses (rabbit, 300mg/kg) which were maternally toxic were also embryotoxic. High doses in rats (320mg/kg) delayed parturition (probably due to an inhibition of prostaglandin synthesis).

The active metabolite of nabumetone 6-MNA is distributed into milk of lactating rats in concentrations approximately equal to those in plasma.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablets also contain:

Microcrystalline cellulose 101 (E460)
Hydroxypropylmethylcellulose (E464)
Sodium lauryl sulfate
Sodium starch glycollate
Colloidal silica
Magnesium stearate

The coating contains:

Hydroxypropylmethylcellulose (E464)
Propylene glycol
Purified talc (E553)
Carmoisine aluminium lake (E122)
Indigo carmine aluminium lake (E132)
Titanium dioxide (E171)

6.2. Incompatibilities

None known.

6.3. Shelf Life

Three years from the date of manufacture.

6.4. Special Precautions for Storage

Store in the original container.

6.5. Nature and Contents of Container

The blister packs are manufactured from 250µm white rigid PVC and 20µm hard temper aluminium foil. The polypropylene containers are manufactured from rigid injection moulded polypropylene with snap-on polyethylene lids.

Pack sizes: 28s, 56s, 84s, 112s (blisters)

6.6. Instruction for Use/Handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8. MARKETING AUTHORISATION NUMBER

PL 00142/0450

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/03/2009

10 DATE OF REVISION OF THE TEXT

07/03/2023