SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Nabumetone 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 500 mg of nabumetone.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablet.
Brown, capsule shaped biconvex tablet plain on both sides.

4. CLINICAL PARTICULARS

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

It is indicated for the treatment of osteoarthritis and rheumatoid arthritis requiring anti-inflammatory and analgesic treatment.

4.2. Posology and method of administration

Posology

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

For severe or persistent symptoms, or during acute exacerbations, an additional one or two tablets (500 mg – 1 g) may be given as a morning dose.
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Elderly

In common with many drugs, blood levels may be higher in elderly patients. The recommended daily dose of two tablets (1 g) should not be exceeded in this age group and in some cases one tablet (500 mg) may give satisfactory relief.
The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patients should be monitored for gastrointestinal bleeding during NSAID therapy.

Children

There are no clinical data to recommend use of Nabumetone tablets in children.

Method of administration

For oral administration.

Nabumetone tablets should be taken preferably with or after food.

4.3 Contraindications

Hypersensitivity to nabumetone or to any of the excipients listed in section 6.1.

Active or history of recurrent peptic ulcer/ GI haemorrhage, perforation or peptic disease (two or more distinct episodes).

NSAID's are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

Severe heart failure, hepatic failure and renal failure (see section 4.4).

During the last trimester of pregnancy and in nursing mothers (see section 4.6).

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

Patients with current cerebrovascular or other haemorrhage.

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).

The use of nabumetone with concomitant NSAIDs, including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

Elderly

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

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. In patients with severe renal impairment (creatinine clearance less than 30 ml/minute): 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).

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.

**Cardiovascular and cerebrovascular effects**

Appropriate monitoring and therapy should be instigated if warranted 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 terms treatment) may by 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, and 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 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 aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).
Patients with a history of GI peptic disease, 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 received concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, NSAIDs, selective serotonin re-uptake inhibitors or anti-platelet agents such as aspirin 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 gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8). In patients with active peptic ulcer, physicians must weigh the benefits of therapy with nabumetone against possible hazards, institute an appropriate ulcer treatment regimen and monitor the patients' progress carefully.

Nabumetone is better tolerated than most other NSAIDs, primarily because it results in fewer effects on the gastrointestinal (GI) system. 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 are lower than those ascribed to other NSAIDs, the prescribing physician should be aware that these ADR can occur even in the absence of previous peptic disease.

Despite the relative gastrointestinal and renal safety of nabumetone, caution should be used when administering to patients with:

- active upper GI ulceration. Appropriate treatment should be instigated prior to initiating nabumetone therapy.

- previous aspirin- 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.

*Systemic lupus erythematosus (SLE) and mixed connective tissue disease*

In patients with SLE and mixed connective tissue disorders, there may be an increased risk of aseptic meningitis (see section 4.8).

*Dermatological*

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy; the onset of the reaction occurring in the majority of cases within the first month of treatment. Nabumetone should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

*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.

NSAIDs could hide signs of infectious disease.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Other analgesics including cyclooxygenase-2 selective inhibitors: avoid the concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4).

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 ARF.

Consequently, hydration and frequent monitoring of these patients is warranted.

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

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

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased elimination of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity.

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

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

Concomitant administration of nabumetone with other protein-bound drugs, e.g. hydantoin anticonvulsants, sulphonamides or sulphonylurea hypoglycaemics should be undertaken with caution and overdosage signals carefully monitored.
Mifepristone: NSAIDs should not be used 8–12 days after mifepristone administration, as NSAIDs can reduce the effect of mifepristone.

Aluminium hydroxide gel, paracetamol, cimetidine and aspirin have not affected the metabolism and bioavailability of Nabumetone tablets in volunteer subjects.

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

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRI's): Increased risk of gastrointestinal bleeding (see section 4.4).

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and hematoma in HIV (+) haemophiliacs receiving concurrent treatment with Zidovudine and ibuprofen.

No specific interaction studies between nabumetone and the above have been performed. Caution is therefore recommended for concomitant therapy with the drugs listed above.

4.6 Fertility, pregnancy and lactation

Pregnancy

No teratogenic effects have been demonstrated in experiments with animals. High doses which were maternally toxic were also embryotoxic (rabbit 300mg/kg dose). High doses in rats (320 mg/kg dose) delayed parturition (thought to be due to inhibition of prostaglandin synthesis).

There is no clinical trial experience with the use of nabumetone during human 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 foetus (risk of closure of the ductus arteriosus, pulmonary and cardiac changes), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and duration of labour increased with an increased bleeding tendency in both mother and child (see section 4.3). 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.

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, 6MNA 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**
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.

4.7. **Effects on ability to drive and use machines**

Undesirable effects such as dizziness, drowsiness, confusion, fatigue, visual 
disturbances are possible after taking NSAIDs. If affected, patients should 
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, not known (cannot be estimated from the available data). 
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: Neutropenia, agranulocytosis, leucopenia, aplastic anaemia and 
haemolytic anaemia.

**Immune system disorders**

Very rare: Anaphylaxis, anaphylactoid reaction

**Psychiatric disorders**

Uncommon: Confusion, nervousness, insomnia
Not known: Depression, hallucinations

**Nervous system disorders**

Uncommon: Somnolence, dizziness, headache, paraesthesia, anxiety
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)), vertigo, drowsiness

**Eye disorders**

Uncommon: Abnormal vision, eye disorder
Not known: Optic neuritis

**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
Not known: Asthma, aggravated asthma, bronchospasm

**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
Very rare: Pancreatitis
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). 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, erythema multiforme, angioedema, pseudoporphyria, alopecia
Not known: Purpura

**Musculoskeletal and connective tissue disorders**
Uncommon: Myopathy

**Renal and urinary disorders**
Uncommon: Urinary tract disorder
Very rare: Renal failure, nephrotic syndrome
Not known: Interstitial nephritis

**Reproductive system and breast disorders**
Very rare: Menorrhagia

**General disorders and administration site conditions**
Common: Oedema
Uncommon: Asthenia, fatigue
Not known: Malaise

**Investigations**
Uncommon: Elevated liver function tests

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 of 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 at: www.mhra.gov.uk/yellowcard

4.9. Overdose

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

Management

There is no specific antidote and the active metabolite 6-MNA is not dialyzable. Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal 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 patients’

5 PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other anti-inflammatory and antirheumatic agents, non-steroids.

ATC Code: M01AX01

Nabumetone contains as active substance 4-(6’-methoxy-2’-naphthyl)-2-butanone

Nabumetone is a non acidic non steroidal anti-inflammatory agent which is a relatively weak inhibitor of prostaglandin synthesis. A notable feature of the animal pharmacology is the lack of effect on the gastric mucosa. Nabumetone has a weak effect on platelet aggregation caused by collagen and no effect on bleeding time.
In humans, lower frequency of peptic ulcers, bleeding or perforation has been reported in comparison with other NSAIDs. Nabumetone is well absorbed from the gastro-intestinal tract and undergoes rapid and extensive metabolism in the liver to 6-methoxy-2-naphthylacetic acid (6-MNA), the principal active metabolite which is a potent inhibitor of prostaglandin synthesis.

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 nabumetone 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.

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 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 1 day in man.

Elderly

The steady-state plasma concentration in the elderly 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**

No data of relevance which is additional to that already included in other sections of the SPC.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

Maize starch  
Sodium Starch Glycollate (Type A)  
Povidone  
Sodium Lauryl Sulphate  
Colloidal Silicon Dioxide  
Magnesium Stearate

Film Coating:  
Hypermellose  
 Titanium dioxide  
Talc  
Red iron oxide  
Glycerol triacetate

6.2 **Incompatibilities**

Not applicable.

6.3 **Shelf life**

3 years.

6.4 **Special precautions for storage**

Do not store above 25°C. Store in the original package.
6.5. Nature and contents of container

Blisters of PVC/PVdC/aluminium.

Pack sizes of 8, 56 and 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Cipla (EU) Limited,
Hillbrow House,
Hillbrow Road,
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8 MARKETING AUTHORISATION NUMBER(S)

PL 36390/0015

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