Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nabumetone Tillomed 500 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg nabumetone.

Excipients with known effect
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.
White, modified capsule shaped, film coated tablets, 17.60mm x 8.10mm, debossed with ''HP'' on one side and ''370'' on the other side.

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
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).
Nabumetone Tillomed should be taken preferably with or after food.

Adult
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.

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.

Paediatric
The safety and efficacy of Nabumetone Tillomed in children has not yet been established. Therefore nabumetone is not recommended for use in children or adolescents under 18 years due to lack of clinical data.

Method of administration
For oral administration.

4.3 Contraindications

• Hypersensitivity to the active substance 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, acetylsalicylic acid 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 severe heart failure and in 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 Tillomed 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 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).

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 required concomitant low dose acetylsalicylic acid, 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 indicative for ulceration (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, anti-coagulants such as warfarin, NSAIDs, selective serotonin re-uptake inhibitors or anti-platelet agents such as aspirin, 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 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 wheigh 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 acetylsalicylic acid, 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.

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).

Dermatological
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 Tillomed 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 ophtalmological examination.

4.5 Interaction with other medicinal products and other forms of interactions

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.

The following commonly available drugs do not affect nabumetone metabolism and bioavailability: paracetamol, ASA, cimetidine, aluminium hydroxide antacids.
Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
Use of more than one NSAID is not recommended.
Lithium: Decreased elimination of lithium.
Methotrexate: Decreased elimination of methotrexate.
Ciclosporin: Increased risk of nephrotoxicity.
Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
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.
Probenecid: Reduction in the metabolism of nabumetone and a reduction in the elimination of nabumetone and metabolites.
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.
Alcohol, bisphosphonates, oxpentifylline (pentoxyfilline) and sulfinpyrazone, may potentiate the GI side-effects and the risk of bleeding or ulceration.
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 heamatoma in HIV(+) haemophiliacs receiving concurrent treatment with Zidovudine and ibuprofen.

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

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

Paediatric population
Interaction studies have only been performed in adults.

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 organogentic period. 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.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

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 unterine contractions resulting in delayed or prolonged labour.
Consequently, nabumetone is contraindicated during the third trimester of pregnancy.

Breastfeeding
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
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, confusion, fatigue and 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/l0), 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.

MedRA System Organ Class	**Frequency**	**Adverse Reaction**
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[1]	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
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
	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

[1]Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or Gastrointestinal 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.

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).

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).

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, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; email: medsafety@hpra.ie.

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.

Therapeutic measure: 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' clinical condition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other anti-inflammatory and antirheumatic agents, non-steroids, ATC code: M01AX01

Mechanism of action
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.

Pharmacodynamic effects
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. 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

Absorption
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 Tillomed is approximately 35% (23-52%). The maximum plasma level of 6-MNA is reached at around 3 (1-12) hours after dosing.

Distribution
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. 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.
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.

Biotransformation
6-MNA is eliminated by metabolism, principally conjugation with glucuronic acid, and o-demethylation followed by conjugation.

Elimination
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

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Cellulose microcrystalline
Sodium starch glycolate (Type A)
Silica colloidal anhydrous
Hypromellose
Sodium lauril sulfate
Magnesium stearate

Coating
Hypromellose
Titanium dioxide (E171)
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 2 years
Once opened, use within 28 days

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottles with white, opaque polypropylene cap each containing 56 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Tillomed Pharma GmbH
Manhagener Allee 36
22926 Ahrensburg
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8 MARKETING AUTHORISATION NUMBER

PA22720/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th July 2017
Date of last renewal: 25th May 2022

10 DATE OF REVISION OF THE TEXT

October 2021