SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trademark 100 mg Tablets
Trademark 100 mg Granules for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100mg nimesulide.
Each sachet contains 100mg nimesulide.

Excipients with known effect: lactose (tablets) and sucrose (granules for oral suspension)
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.
White/light yellow round tablets.

Granules for oral suspension.
Yellow granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute pain (see section 4.2)
Primary dysmenorrhoea

Nimesulide should only be prescribed as second line treatment. The decision to prescribe nimesulide should be based on assessment of the individual patient's overall risks (see section 4.3 and 4.4).

4.2 Posology and method of administration

Posology:

Trademark 100mg Tablets (or 100mg Granules) should be used for the shortest possible duration, as required by the clinical situation. Moreover, undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (see section 4.4).

The maximum duration of a treatment course with nimesulide is 15 days.

Adults:
Tablets or Granules: one 100mg tablet (or sachet) twice a day.

Elderly:
In elderly patients there is no need to reduce the daily dosage (see section 5.2).

Children (< 12 years):
Trademark 100mg Tablets (or 100mg Granules) is contraindicated in these patients (see also section 4.3).

Adolescents (from 12 to 18 years):

On the basis of the kinetic profile in adults and on the pharmacodynamic characteristics of nimesulide, no dosage adjustment in these patients is necessary.

Impaired renal function:
On the basis of pharmacokinetics, no dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance of 30-80 ml/min), while *Trademark* 100mg Tablets (or 100mg Granules) is contraindicated in case of severe renal impairment (creatinine clearance < 30ml/min) (see sections 4.3 and 5.2).

Hepatic impairment:
The use of *Trademark* 100mg Tablets (or 100mg Granules) is contraindicated in patients with hepatic impairment (see sections 4.3 and 5.2).

Method of administration
Oral use.
Trademark 100mg Granules: The granules should be dissolved in a glass of water.
Trademark 100mg Tablets (or 100mg Granules) are recommended to be taken after meals.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- History of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria, nasal polyps) in response to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs,
- History of hepatotoxic reactions to nimesulide,
- Concomitant exposure to other potentially hepatotoxic substances,
- Alcoholism, drug addiction,
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy,
- Active, or history of recurrent peptic ulcer / haemorrhage (two or more distinct episodes of proven ulceration or bleeding),
- Cerebrovascular bleeding or other active bleeding or bleeding disorders,
- Severe coagulation disorders,
- Severe heart failure,
- Severe renal impairment,
- Hepatic impairment,
- Patients with fever and / or flu-like symptoms,
- Children under 12 years,
- The third trimester of pregnancy and breastfeeding (see sections 4.6 and 5.3).

4.4 Special warnings and precautions for use

The use of *Trademark* 100mg Tablets (or 100mg Granules) with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided. In addition, patients should be advised to refrain from other concomitant analgesics.

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (see section 4.2).

Treatment should be discontinued if no benefit is seen.

Hepatic effects
Rarely *Trademark* 100mg Tablets (or 100mg Granules) has been reported to be associated with serious hepatic reactions, including very rare fatal cases (see also section 4.8). Patients who experience symptoms compatible with hepatic injury during treatment with *Trademark* 100mg Tablets (or 100mg Granules) (e.g. anorexia, nausea, vomiting, abdominal pain, fatigue, dark urine) or patients who develop abnormal liver function tests should have treatment discontinued. These patients should not be

rechallenged with nimesulide. Liver damage, in most cases reversible, has been reported following short exposure to the drug.

Patients receiving nimesulide who develop fever and /or flu-like symptoms should discontinue treatment.

Gastrointestinal effects
Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of 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 toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding), particularly in the initial stages of treatment.

Gastrointestinal bleeding or ulceration / perforation can occur at any time during treatment with or without warning symptoms or a previous history of gastrointestinal events. If gastrointestinal bleeding or ulceration occurs, nimesulide should be discontinued. Nimesulide should be used with caution in patients with gastrointestinal disorders, including history of peptic ulceration, history of gastrointestinal haemorrhage, ulcerative colitis or Crohn's disease.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or antiplatelet agents such as acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving *Trademark* 100mg Tablets (or 100mg Granules), 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 their condition may be exacerbated (see section 4.8 – undesirable effects).

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). Therefore, appropriate clinical monitoring is advisable.

Cardiovascular and cerebrovascular effects
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example, myocardial infarction or stroke). There are insufficient data to exclude such a risk for *Trademark*.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with *Trademark* 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).

As nimesulide can interfere with platelet function, it should be used with caution in patients with bleeding diathesis (see also section 4.3). However, *Trademark* 100mg Tablets (or 100mg Granules) are not a substitute for acetylsalicylic acid for cardiovascular prophylaxis.

Renal effects
In patients with renal or cardiac impairment, caution is required since the use of *Trademark* 100mg Tablets (or 100mg Granules) may result in deterioration of renal function. In the event of deterioration, the treatment should be discontinued (see also section 4.5).

Skin Reactions
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 of 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. *Trademark* 100mg Tablets (or 100mg Granules) should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Fertility effects
The use of *Trademark* 100mg Tablets (or 100mg Granules) 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 *Trademark* 100mg Tablets (or 100mg Granules) should be considered (see section 4.6).

Trademark 100mg Tablets contain lactose, therefore patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Trademark 100mg Granules contains sucrose, therefore patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions.

Other non-steroidal anti-inflammatory drugs (NSAIDs):
The combined use of *Trademark* (see section 4.4) with other non-steroidal anti-inflammatory drugs, including acetylsalicylic acid given at anti-inflammatory doses (≥ 1g as single intake or ≥ 3g as total daily amount) is not recommended.

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). Patients receiving warfarin or similar anticoagulant agents have an increased risk of bleeding complications, when treated with *Trademark* 100mg Tablets (or 100mg Granules). Therefore this combination is not recommended (see also section 4.4.) and is contraindicated in patients with severe coagulation disorders (see also section 4.3). If the combination cannot be avoided, anticoagulant activity should be monitored closely.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Diuretics, Angiotensin Conversion Enzyme Inhibitors (ACE inhibitors) and Angiotensin II Antagonists (AIIA):
NSAIDs may reduce the efficacy of diuretics and that of other antihypertensive drugs. In some patients with reduced renal function (e.g. dehydrated patients or elderly subjects with impairment of renal function), concomitant administration of an ACE inhibitor and cyclo-oxygenase inhibitors may result in progression of the deterioration of renal function, including the possibility of acute renal insufficiency, which is normally reversible.

The occurrence of these interactions should be taken into consideration in patients who have to take *Trademark* 100mg Tablets (or 100mg Granules) in association with ACE inhibitors or AIIA. Consequently, this drug association should be administered with precaution, especially in elderly patients. Patients should be properly hydrated, and the need for monitoring of renal function after starting the concomitant treatment and periodically after that should be analysed.

Pharmacokinetic interactions: effect of nimesulide on the pharmacokinetics of other drugs.

Furosemide:
In healthy subjects, nimesulide transiently decreases the effect of furosemide on sodium excretion and, to a lesser extent, on potassium excretion and reduces the diuretic response.
Co-administration of nimesulide and furosemide results in a decrease (of about 20%) of the AUC and cumulative excretion of furosemide, without affecting its renal clearance.
The concomitant use of furosemide and *Trademark* 100mg Tablets (or 100mg Granules) requires caution in susceptible renal or cardiac patients, as described under section 4.4.

Lithium:
Non-steroidal anti-inflammatory drugs have been reported to reduce the clearance of lithium, resulting in elevated plasma levels and lithium toxicity. If *Trademark* 100mg Tablets (or 100mg Granules) are prescribed for a patient receiving lithium therapy, lithium levels should be monitored closely.

Potential pharmacokinetic interactions with glibenclamide, theophylline, warfarin, digoxin, cimetidine and an antacid preparation (i.e. a combination of aluminium and magnesium hydroxide) were also studied in vivo. No clinically significant interactions were observed.

Nimesulide inhibits CYP2C9. The plasma concentrations of drugs that are substrates of this enzyme may be increased when *Trademark* 100mg Tablets (or 100mg Granules) are used concomitantly.
Caution is required if nimesulide is used less than 24 hours before or after treatment with methotrexate because the serum level of methotrexate might increase and therefore, the toxicity of this drug might increase.
Due to their effect on renal prostaglandins, prostaglandin synthetase inhibitors like nimesulide may increase the nephrotoxicity of cyclosporins.

Pharmacokinetic Interactions: Effects of other drugs on the pharmacokinetics of nimesulide:

In vitro studies have shown displacement of nimesulide from binding sites by tolbutamide, salicylic acid and valproic acid.
However, despite a possible effect on plasma levels, these interactions have not demonstrated clinical significance.

4.6 Fertility, pregnancy and lactation

Pregnancy and Fertility:

The use of *Trademark* 100mg Tablets (or 100mg Granules) is contraindicated in the third trimester of pregnancy (see section 4.3).
Like other NSAIDs *Trademark* 100mg Tablets (or 100mg Granules) is not recommended in women attempting to conceive (see section 4.4).

Inhibition of prostaglandin synthesis may have a negative impact on pregnancy and/or embryonic/fetal development. Results of epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after the use of an inhibitor of prostaglandin synthesis in the first stage of pregnancy. The absolute risk for cardiac malformations was increased from less than 1% to approximately 1.5%. The risk has been considered to increase with the dose and duration of treatment.

In animals, administration of inhibitors of prostaglandin synthesis has been shown to provoke an increase in pre- and post-implantation loss and in embryonic-fetal mortality. Furthermore, an increased

incidence of various malformations, including the cardiovascular one, has been reported in animals to which inhibitors of prostaglandin synthesis were administered during the period of organogenesis.

Studies in rabbits have shown an atypical reproductive toxicity (see section 5.3) and no adequate data from the use of *Trademark* 100mg Tablets (or 100mg Granules) in pregnant women are available. Therefore, the potential risk for humans is unknown and prescribing the drug during the first two trimesters of pregnancy is not recommended, except in cases where it is strictly necessary.

If *Trademark* 100mg Tablets (or 100mg Granules) are used by a woman who is trying to conceive, or during the first and second trimesters of pregnancy, the dose and duration of treatment should be kept as low as possible.

During the third trimester of pregnancy, all inhibitors of prostaglandin synthesis may expose

- the fetus to:
  - cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
  - renal dysfunction, which may progress to renal insufficiency with oligohydramnios;
- the mother and the newborn infant, at the end of pregnancy, to:
  - possible prolongation of bleeding time, and an antiplatelet effect which may occur even at very low doses;
  - inhibition of uterine contractions resulting in delay or prolongation of labour.

Consequently, *Trademark* 100mg Tablets (or 100mg Granules) is contraindicated during the third trimester of pregnancy.

Breastfeeding:

It is not known whether nimesulide is excreted in human milk. *Trademark* 100mg Tablets (or 100mg Granules) is contraindicated when breastfeeding (see sections 4.3 and 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effect of *Trademark* 100mg Tablets (or 100mg Granules) on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence after receiving *Trademark* 100mg Tablets (or 100mg Granules) should refrain from driving or operating machines.

4.8 Undesirable effects

a) General description

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) (see section 4.4).

Oedema, hypertension, and cardiac failure have been reported in association with NSAID treatment. Very rare cases of bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis have been reported.

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 - Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

b) Table of adverse reactions

The following listing of undesirable effects is based on data from controlled clinical trials (approximately 7,800 patients) and from post marketing surveillance with reporting rates classified as: very common (>1/10); common (>1/100, <1/10), uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000), including isolated cases.

Blood disorders	Rare	Anaemia* Eosinophilia*
	Very rare	Thrombocytopenia Pancytopenia Purpura
Immune system disorders	Rare	Hypersensitivity*
	Very rare	Anaphylaxis
Metabolism and nutrition disorders	Rare	Hyperkalaemia*
Psychiatric disorders	Rare	Anxiety* Nervousness* Nightmare*
Nervous system disorders	Uncommon	Dizziness*
	Very rare	Headache Somnolence Encephalopathy (Reye's syndrome)
Eye disorders	Rare	Vision blurred*
	Very rare	Visual disturbance
Ear and labyrinth disorders	Very rare	Vertigo
Cardiac disorders	Rare	Tachycardia*
Vascular disorders	Uncommon	Hypertension*
	Rare	Haemorrhage* Blood pressure fluctuation* Hot flushes*
Respiratory disorders	Uncommon	Dyspnoea*
	Very rare	Asthma Bronchospasm
Gastrointestinal disorders	Common	Diarrhoea* Nausea* Vomiting*
	Uncommon	Constipation* Flatulence* Gastrointestinal bleeding Duodenal ulcer and perforation Gastric ulcer and perforation
	Very rare	Gastritis* Abdominal pain Dyspepsia Stomatitis Melaena
Hepato-biliary disorders (see section 4.4."Special warnings and special precautions for use")	Common	Hepatic enzymes increased*
	Very rare	Hepatitis Fulminant hepatitis (including fatal cases) Jaundice Cholestasis
Skin and subcutaneous tissue disorders	Uncommon	Pruritus* Rash* Sweating increased*

	Rare	Erythema* Dermatitis*
	Very rare	Urticaria Angioneurotic oedema Face oedema Erythema multiforme Stevens Johnson syndrome Toxic epidermal necrolysis
Renal and urinary disorders	Rare	Dysuria* Haematuria*
	Very rare	Urinary retention* Renal failure Oliguria Interstitial nephritis
General disorders	Uncommon	Oedema*
	Rare	Malaise* Asthenia*
	Very rare	Hypothermia

**frequency based on clinical trial*

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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. No information is available regarding the removal of nimesulide by haemodialysis, but based on its high degree of plasma protein binding (up to 97.5%) dialysis is unlikely to be useful in overdose. Emesis and/or activated charcoal (60 to 100 g in adults) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, haemodialysis, or haemoperfusion may not be useful due to high protein binding. Renal and hepatic function should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
ATC code: M01AX17

Nimesulide is a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties which acts as an inhibitor of prostaglandin synthesis enzyme cyclo-oxygenase.

5.2 Pharmacokinetic properties

Tablets and Granules
Nimesulide is well absorbed when given per o.s. After a single dose of 100mg nimesulide a peak plasma level of 3-4 mg/l is reached in adults after 2-3 hours. AUC = 20 - 35 mg h/l. No statistically significant difference has been found between these figures and those seen after 100mg given twice daily for 7 days.

Up to 97.5% binds to plasma proteins**.**

Nimesulide is extensively metabolised in the liver following multiple pathways, including cytochrome P450 (CYP) 2C9 isoenzymes. Therefore, there is the potential for a drug interaction with concomitant administration of drugs which are metabolised by CYP2C9 (see under section 4.5). The main metabolite is the para-hydroxy derivative which is also pharmacologically active. The lag time before the appearance of this metabolite in the circulation is short (about 0.8 hour) but its formation constant is not high and is considerably lower than the absorption constant of nimesulide. Hydroxynimesulide is the only metabolite found in plasma and it is almost completely conjugated. $T_{½}$ is between 3.2 and 6 hours.

Nimesulide is excreted mainly in the urine (approximately 50% of the administered dose).
Only 1-3% is excreted as the unmodified compound. Hydroxynimesulide, the main metabolite is found only as a glucuronate. Approximately 29% of the dose is excreted after metabolism in the faeces.

The kinetic profile of nimesulide was unchanged in the elderly after acute and repeated doses.

In an acute experimental study carried out in patients with mild to moderate renal impairment (creatinine clearance 30-80 ml/min) versus healthy volunteers, peak plasma levels of nimesulide and its main metabolite were not higher than in healthy volunteers. AUC and t1/2 beta were 50% higher, but were always within the range of kinetic values observed with nimesulide in healthy volunteers. Repeated administration did not cause accumulation.
Nimesulide is contra-indicated in patients with hepatic impairment (see section 4.3).

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
In repeated dose toxicity studies, nimesulide showed gastrointestinal, renal and hepatic toxicity.
In reproductive toxicity studies, embryotoxic and teratogenic effects (skeletal malformations, dilatation of cerebral ventricles) were observed in rabbits, but not in rats, at maternally non-toxic dose levels. In rats, increased mortality of offspring was observed in the early postnatal period and nimesulide showed adverse effects on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets: Magnesium Stearate, Docusate Sodium, Hyprolose, Lactose monohydrate, Sodium Starch Glycollate, Microcrystalline Cellulose, Hydrogenated Vegetable Oil.

Granules: Sucrose, Maize Starch, Glucose Liquid Spray Dried, macrogol cetostearyl ether, Citric Acid Anhydrous, Orange flavor.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Tablets: 5 years.

Granules: 5 years.

6.4 Special precautions for storage

Tablets and Granules: This medicinal product does not require any special storage conditions.

6.5 Nature and contents of the container

Tablets: PVC blisters heat-sealed to aluminium foil. Boxes of 6, 9, 10, 15, 20, 30 tablets.
Not all pack sizes may be marketed.

Granules: Sachet laminate consisting of aluminium, paper and polyethylene or aluminium, paper, polyethylene and Surlyn. Boxes of 6, 9, 14, 15, 18 and 30 sachets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

08/2020

LABELLING

TABLETS

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Trademark 100 mg Tablets
nimesulide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Composition: 1 tablet contains nimesulide 100mg.

3. LIST OF EXCIPIENTS

Excipients: docusate sodium, hydroxypropyl cellulose, lactose monohydrate, sodium starch glycollate Type A, microcrystalline cellulose, hydrogenated vegetable oil, magnesium stearate.

4. PHARMACEUTICAL FORM AND CONTENTS

<[To be completed nationally]>

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Attention: for use carefully read the leaflet.
The expiry date refers to the product correctly stored in the unopened container.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Do not dispose of in the environment after use.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

15. INSTRUCTIONS ON USE

Indications, posology and mode of use: see the leaflet.

16. INFORMATION IN BRAILLE

Trademark 100mg Tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifer included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Trademark 100 mg Tablets
nimesulide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

LABELLING

GRANULES

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Trademark 100 mg Granules for Oral Suspension
nimesulide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Composition: 1 sachet contains nimesulide 100mg

3. LIST OF EXCIPIENTS

Excipients: Sucrose, Maize Starch, Glucose Liquid Spray Dried, macrogol cetostearyl ether, Citric Acid Anhydrous, Orange flavour

4. PHARMACEUTICAL FORM AND CONTENTS

<[To be completed nationally]>

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Attention: for use carefully read the leaflet.
The expiry date refers to the product correctly stored in the unopened container.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Do not dispose of in the environment after use.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

15. INSTRUCTIONS ON USE

Indications, posology and mode of use: see the leaflet.

16. INFORMATION IN BRAILLE

Trademark 100mg Granules

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifer included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

SACHET

1. NAME OF THE MEDICINAL PRODUCT

Trademark 100 mg Granules for Oral Suspension
nimesulide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

For oral use.
Composition: 1 sachet contains nimesulide 100mg.
Excipients: Sucrose, Maize Starch, Glucose Liquid Spray Dried, macrogol cetostearyl ether, Citric Acid Anhydrous, Orange flavour.
Keep out of the sight and reach of children.
Do not dispose of in the environment after use.
MA Number <[To be completed nationally]>.

PACKAGE LEAFLET

Package Leaflet: Information for the user

***Trademark* 100 mg Tablets**
***Trademark* 100 mg Granules for oral suspension**

nimesulide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What *Trademark* is and what it is used for

Trademark is a non-steroidal anti-inflammatory drug ("NSAID") with pain-killing properties. It is used for the treatment of acute pain and for the treatment of period pains.

Before prescribing *Trademark*, your doctor will assess the benefits this medicine may give you against your risks of developing side effects.

2. What you need to know before you take *Trademark*

Do not use *Trademark*:

- if you are allergic to nimesulide or to any of the other ingredients of this medicine (listed in section 6);
- if you have had any of the following signs after taking acetylsalicylic acid or other NSAIDs:
  - wheezing, chest tightness, breathlessness (asthma)
  - nasal blockage due to swellings in the lining in your nose (nasal polyps)
  - skin rashes / nettles rash (urticaria)
  - sudden skin or mucosal swelling, such as swelling around the eyes, face, lips, mouth or throat, possibly making breathing difficult (angioneurotic oedema);
- after previous therapy with NSAIDs and history of
  - bleeding in your stomach or intestines,
  - holes (perforations) in your stomach or intestines;
- recent or history of stomach or intestinal ulcers or bleeding (ulceration or bleeding occurring at least twice);
- have had bleeding into the brain (a stroke);
- have any other problem with bleeding or any problems due to your blood not clotting;
- impaired liver function;
- are taking other medicines that are known to affect liver, e.g. paracetamol or any other pain-killer or NSAID treatment,

- are taking drugs of addiction, or have developed a habit that makes you dependent on drugs or other substances,
- are a regular heavy drinker (alcohol),
- had a reaction to nimesulide affecting the liver in the past,
- non dialysed severe kidney failure,
- severe heart failure,
- are suffering from fever or flu (feeling generally achy, unwell, chills or shivering or have a temperature),
- are in the last 3 months of pregnancy;
- are breastfeeding.

Do not give *Trademark* to a child aged less than 12.

Warnings and precautions
Talk to your doctor or pharmacist before taking *Trademark*.

Medicines such as *Trademark* may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment.

If you have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.

If you develop severe allergic reactions, you should discontinue *Trademark* at first appearance of skin rash, lesions of soft tissues (mucosal lesions), or any other sign of allergy, and contact your doctor.

Stop your treatment with *Trademark* immediately as soon as you notice bleeding (causing tar-coloured stools) or ulceration of your digestive tract (causing abdominal pain).

Take special care with *Trademark*
If during nimesulide treatment you develop symptoms that suggest a liver condition, you should stop taking nimesulide and inform your doctor immediately. Symptoms suggesting a liver condition include loss of appetite, nausea, vomiting, abdominal pain, persistent tiredness or dark urine.

If you have ever suffered from peptic ulcers, bleeding from the stomach or bowel, or from inflammatory conditions of the bowel such as ulcerative colitis or Crohn's disease, you should tell your doctor before taking *Trademark*.

If during treatment with *Trademark*, you develop fever and/or flu-like symptoms (feeling generally achy unwell and chills or shivering), you should stop taking the product and inform your doctor.

If you suffer from any mild heart disease, high blood pressure, circulatory or kidney problems, tell your doctor before taking *Trademark*.

If you are elderly, your doctor may want to see you at intervals to make sure that *Trademark* is not causing stomach, kidney, heart or liver problems.

If you are planning a pregnancy, you should inform your doctor since *Trademark* may decrease fertility.

If you have an intolerance to some sugars, you should contact your doctor before taking this medicine.

Other medicines and *Trademark*
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

If you are taking any of the following as they may interact with *Trademark*:
- corticosteroids (medicines used in the treatment of inflammatory conditions),

- medicine to thin the blood (anti-coagulants e.g. warfarin, or antiplatelet agents, acetylsalicylic acid or other salicylates),
- antihypertensives or diuretics (medicines to control blood pressure or heart conditions),
- lithium which is used to treat depression and similar conditions,
- selective serotonin reuptake inhibitors (medicines to treat depression),
- methotrexate (medicine used for the treatment of rheumatoid arthritis and cancer),
- cyclosporine (medicine used after transplantation or for the treatment of immune system disorders),

make sure that your doctor or pharmacist knows that you are taking these medicines before you start taking *Trademark*.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- *Trademark* must not be used during the last 3 months of pregnancy: it can cause problems for the baby and for labour.
- If you are planning a pregnancy, you should inform your doctor since *Trademark* may decrease fertility.
- If you are in the first or second trimester of pregnancy, do not exceed the dose and duration of treatment prescribed by your doctor.

Trademark must not be used during breastfeeding.

Driving and using machines
Do not drive or use machines if *Trademark* makes you dizzy or sleepy.

***Trademark* 100mg Tablets contain lactose**
***Trademark* 100mg Granules contains sucrose**
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take *Trademark*

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms.

Adults and adolescents from 12 years of age
The recommended dose is one 100 mg tablet or one 100 mg sachet twice a day.

Use *Trademark* for the shortest period of time as possible and for not more than 15 days in any single course of treatment.

Method of administration:
Trademark 100mg Granules: Dissolve the granules in a glass of water.
Trademark 100mg Tablets (or 100mg Granules): Take the tablets (or granules) after meals.

If you take more *Trademark* than you should:

If you take or think that you have taken more *Trademark* than you should (overdose), contact your doctor or hospital without delay. Bring any remaining medicine with you. In case of overdose, you will probably develop one of the following symptoms: drowsiness, nausea, stomach pain, stomach bleeding or difficulty breathing.

If you forget to take *Trademark*:

Do not take a double dose to make up for forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If any of the following symptoms occur, stop taking the medicine and tell your doctor immediately, since these may indicate rare severe side effects that require urgent medical attention:
- stomach discomfort or pain, loss of appetite, nausea (feeling sick), vomiting or bleeding from your stomach or bowel or passing black motions
- skin disorders such as rash or redness
- wheezing or shortness of breath
- yellowing of your skin or the whites of your eyes (jaundice)
- unexpected change in the amount or colour of urine
- swelling of your face, feet or legs
- persistent tiredness.

General side effects of non-steroidal anti-inflammatory medicines (NSAIDs):

The use of some non-steroidal anti-inflammatory drugs (NSAIDs) may be associated with a small increased risk of occlusion of arterial vessels (arterial thrombotic events), e.g. heart attack (myocardial infarction) or stroke (apoplexy), particularly at high doses and in long term treatment.

Fluid retention (oedema), high blood pressure (hypertension) and heart failure (cardiac failure) have been reported in association with NSAID treatment.

The most commonly-observed side effects affect the digestive tract (gastrointestinal events):
- ulcers of the stomach and upper part of the small bowels (peptic/gastroduodenal ulcers)
- a hole in the wall of the bowels (perforation) or bleeding of the digestive tract (sometimes fatal, particularly in the elderly).

Side effects that may occur with *Trademark* are:

- Common (which may affect more than 1 person in 100): diarrhoea, sickness, vomiting, minor changes in blood tests for liver function.
- Uncommon (which may affect up to 1 person in 100): shortness of breath, dizziness, increased blood pressure, constipation, wind, stomach inflammation (gastritis), itching, rash, sweating, swelling (oedema), bleeding from stomach or bowel; duodenal or stomach ulcers and burst ulcers.
- Rare (which may affect less than 1 person in 1,000): anaemia, decrease in white cells in the blood, increase in certain white cells (eosinophils) in the blood, changes in blood pressure, bleeding, discomfort passing urine or stoppage of urine, blood in the urine, increase in potassium in the blood, feelings of anxiety or nervousness, nightmares, blurring of vision, increased pulse rate, skin flushing, redness of the skin, skin inflammation (dermatitis), feeling generally unwell; tiredness.
- Very rare (which may affect up to 1 person in 10,000): severe skin reaction (known as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis) causing skin blistering and feeling very unwell; kidney failure or inflammation (nephritis); disorder of brain function (encephalopathy), decrease in platelets in the blood causing bleeding under the skin or in other parts of the body; black stools due to bleeding; liver inflammation (hepatitis), sometimes very severe causing jaundice and stoppage of bile flow; allergies, including severe reactions with collapse and wheezing; asthma; decrease in body temperature; dizziness, headaches, sleepiness; stomach pain; indigestion; sore mouth; itchy rash (hives); swelling of the face and surrounding areas, visual disturbances.

Medicines such as *Trademark* may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store *Trademark*

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and/or blister and carton after EXP. The expiry date refers to the last day of that month.

Trademark 100mg Tablets and *Trademark* 100mg Granules: This medicinal product does not require any special storage conditions.

6. Contents of the pack and other information

What *Trademark* contains

The active substance is nimesulide.
The other ingredients are:

Trademark 100mg Tablets: Docusate sodium, Hydroxypropylcellulose, Lactose monohydrate, Sodium starch glycolate, Microcrystalline cellulose, Hydrogenated vegetable oil, Magnesium stearate.

Trademark 100mg Granules: Sucrose, Maize Starch, Glucose liquid, spray dried, macrogol cetostearyl ether, Citric acid anhydrous, Orange flavour.

What *Trademark* looks like and contents of the pack

Tablets: White / light yellow round tablets contained in PVC blisters heat-sealed to aluminium foil. Boxes of 6, 9, 10, 15, 20, 30 tablets. Not all pack sizes may be marketed.

Granules: Yellow granular powder contained in 2g sachet. Sachet laminate consists of aluminium, paper and polyethylene or aluminium, paper, polyethylene and Surlyn®. Boxes of 6, 9, 14, 15, 18 and 30 sachets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Marketing Authorisation Holder:
<[To be completed nationally]>

Manufacturer:
Trademark 100mg Tablets:
Helsinn Birex Pharmaceuticals Ltd., Damastown, Mulhuddart, Dublin 15, Ireland.
Vianex S.A - Plant B, 15th Km Marathonos Avenue, 153 51 Pallini Attiki, Athens, Greece Mipharm S.p.A., Via Bernardo Quaranta, 12, 20141 – Milano (MI), Italy.
Patheon Italia S.p.A, Viale G.B. Stucchi 110, 20900 Monza (MB), Italy.

Trademark 100mg Granules:
Helsinn Birex Pharmaceuticals Ltd., Damastown, Mulhuddart, Dublin 15, Ireland.
Mipharm S.p.A., Via Bernardo Quaranta, 12, 20141 – Milano (MI), Italy.
Patheon Italia S.p.A , Viale G.B. Stucchi 110, 20900 Monza (MB), Italy.
Angelini Pharma Česká Republika s.r.o., Páteřní 7, 635 00 Brno, Czech Republic.

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