

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note: This SPC is the one that was annexed to the Commission Decision on this Article 31 referral for nimesulide containing medicinal products. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

**NIMESULIDE 100 MG TABLETS, SOLUBLE TABLETS, EFFERVESCENT TABLETS,
COATED TABLETS, CAPSULES, HARD CAPSULES,
NIMESULIDE 50/100 MG GRANULES OR POWDER FOR ORAL SUSPENSION
NIMESULIDE 1%, 2% OR 5% ORAL SUSPENSION**

1. NAME OF THE MEDICINAL PRODUCT

<TRADENAME>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet, soluble tablet, effervescent tablet, coated tablet, capsule, hard capsule contains 100mg nimesulide.

Each sachet contains 50 or 100mg nimesulide.

Oral suspension containing 10mg, 20mg or 50mg per ml.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet, soluble tablet, effervescent tablet or coated tablet: <Company-specific>

Granules or powder for oral suspension: <Company-specific>

Capsule, hard capsule: <Company-specific>

Oral suspension: <Company-specific>

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute pain.

Symptomatic treatment of painful osteoarthritis.

Primary dysmenorrhoea.

4.2 Posology and method of administration

<Nimesulide-containing medicinal products> should be used for the shortest possible duration, as required by the clinical situation.

Adults:

100mg nimesulide tablets, soluble tablets, effervescent tablets, coated tablets, capsules, hard capsules, 50mg and 100mg granules or powder, 1%, 2% and 5% oral suspension: 100mg bid after meal

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

Children (< 12 years): <Nimesulide containing medicinal products> are 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 <Nimesulide containing medicinal products> are contraindicated in case of severe renal impairment (creatinine clearance < 30ml/min) (see sections 4.3 and 5.2).

Hepatic impairment: the use of <Nimesulide containing medicinal products> is contraindicated in patients with hepatic impairment (see section 5.2).

4.3 Contraindications

Known hypersensitivity to nimesulide or to any of the excipients of the products.
History of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) in response to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
History of hepatotoxic reactions to nimesulide
Active gastric or duodenal ulcer, a history of recurrent ulceration or gastrointestinal bleeding, cerebrovascular bleeding or other active bleeding or bleeding disorders.
Severe coagulation disorders.
Severe heart failure
Severe renal impairment.
Hepatic impairment.
Children under 12 years.
The third trimester of pregnancy and breastfeeding (see sections 4.6 and 5.3).

4.4 Special warnings and special precautions for use

The risk of undesirable effects may be reduced by using <Nimesulide-containing medicinal products> for the shortest possible duration.

Treatment should be discontinued if no benefit is seen.

Rarely <Nimesulide-containing medicinal products> have 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 <Nimesulide-containing medicinal products> (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.

Concomitant administration with known hepatotoxic drugs, and alcohol abuse must be avoided during treatment with <Nimesulide-containing medicinal products> treatment, since either may increase the risk of hepatic reactions.

During therapy with <Nimesulide-containing medicinal products>, patients should be advised to refrain from other analgesics. Simultaneous use of different NSAIDs is not recommended.

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.

In patients with renal or cardiac impairment, caution is required since the use of <Nimesulide-containing medicinal products> may result in deterioration of renal function. In the event of deterioration, the treatment should be discontinued (see also section 4.5).

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including gastrointestinal haemorrhage and perforation, impaired renal, cardiac and hepatic function. Therefore, appropriate clinical monitoring is advisable.

As nimesulide can interfere with platelet function, it should be used with caution in patients with bleeding diathesis (see also section 4.3). However, <Nimesulide-containing medicinal products> is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis.

NSAIDs may mask the fever related to an underlying bacterial infection.

The use of <Nimesulide-containing medicinal products> 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 <Nimesulide-containing medicinal products> should be considered (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Patients receiving warfarin or similar anticoagulant agents or acetylsalicylic acid have an increased risk of bleeding complications, when treated with <Nimesulide-containing medicinal products>. 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.

Pharmacodynamic/pharmacokinetic interactions with diuretics

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 <Nimesulide containing medicinal products> requires caution in susceptible renal or cardiac patients, as described under section 4.4.

Pharmacokinetic interactions with other drugs:

Non-steroidal anti-inflammatory drugs have been reported to reduce the clearance of lithium, resulting in elevated plasma levels and lithium toxicity. If <Nimesulide containing medicinal products> 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 <Nimesulide containing medicinal products> 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 prostaglandines, prostaglandin synthetase inhibitors like nimesulide may increase the nephrotoxicity of cyclosporines.

Effects of other drugs on 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 Pregnancy and lactation

The use of <Nimesulide containing medicinal products> is contraindicated in the third trimester of pregnancy (see section 4.3).

Like other NSAIDs <Nimesulide containing medicinal products> is not recommended in women attempting to conceive (see section 4.4). As with other NSAIDs, known to inhibit prostaglandin synthesis, nimesulide may cause premature closure of the ductus arteriosus, pulmonary hypertension, oliguria, oligoamnios, increased risk of bleeding, uterine inertia and peripheral oedema. There have been isolated reports of renal failure in neonates born to women taking nimesulide in late pregnancy.

Studies in rabbits have shown an atypical reproductive toxicity (see section 5.3) and no adequate data from the use of nimesulide-containing medicinal products 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.

Lactation:

It is not known whether nimesulide is excreted in human milk. <Nimesulide containing medicinal products> are 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 <Nimesulide containing medicinal products> on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence after receiving <Nimesulide containing medicinal products> should refrain from driving or operating machines.

4.8 Undesirable effects

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.

<i>Blood disorders</i>	Rare	Anaemia* Eosinophilia*
	Very rare	Thrombocytopenia Pancytopenia Purpura
<i>Immune system disorders</i>	Rare	Hypersensitivity*
	Very rare	Anaphylaxis
<i>Metabolism and nutrition disorders</i>	Rare	Hyperkalaemia*
<i>Psychiatric disorders</i>	Rare	Anxiety* Nervousness* Nightmare*
<i>Nervous system disorders</i>	Uncommon	Dizziness*
	Very rare	Headache Somnolence Encephalopathy (Reye's syndrome)
<i>Eye disorders</i>	Rare	Vision blurred*
	Very rare	Visual disturbance
<i>Ear and labyrinth disorders</i>	Very rare	Vertigo
<i>Cardiac disorders</i>	Rare	Tachycardia*
<i>Vascular disorders</i>	Uncommon	Hypertension*
	Rare	Haemorrhage* Blood pressure fluctuation* Hot flushes*
<i>Respiratory disorders</i>	Uncommon	Dyspnoea*
	Very rare	Asthma Bronchospasm
<i>Gastrointestinal disorders</i>	Common	Diarrhoea* Nausea* Vomiting*
	Uncommon	Constipation* Flatulence* Gastritis*

	Very rare	Abdominal pain Dyspepsia Stomatitis Melaena Gastrointestinal bleeding Duodenal ulcer and perforation Gastric ulcer and perforation
<i>Hepato-biliary disorders</i> (see section 4.4. "Special warnings and special precautions for use")	Very rare	Hepatitis Fulminant hepatitis (including fatal cases) Jaundice Cholestasis
<i>Skin and subcutaneous tissue disorders</i>	Uncommon	Pruritus* Rash* Sweating increased*
	Rare	Erythema* Dermatitis*
	Very rare	Urticaria Angioneurotic oedema Face oedema Erythema multiforme Stevens Johnson syndrome Toxic epidermal necrolysis
<i>Renal and urinary disorders</i>	Rare	Dysuria* Haematuria* Urinary retention*
	Very rare	Renal failure Oliguria Interstitial nephritis
<i>General disorders</i>	Uncommon	Oedema*
	Rare	Malaise* Asthenia*
	Very rare	Hypothermia
<i>Investigations</i>	Common	Hepatic enzymes increased*
*frequency based on clinical trial		

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

Nimesulide is well absorbed when given by mouth. 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. $T_{1/2}$ 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 $t_{1/2}$ 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

6.2 Incompatibilities

- 6.3 Shelf life**
- 6.4 Special precautions for storage**
- 6.5 Nature and contents of the container**
- 6.6 Instructions for use/handling**

- 7. MARKETING AUTHORISATION HOLDER**

- 8. MARKETING AUTHORISATION NUMBER**

- 9. DATE OF FIRST AUTHORISATION /RENEWAL OF AUTHORISATION**

- 10. DATE OF (PARTIAL) REVISION OF THE TEXT**

SUMMARY OF PRODUCT CHARACTERISTICS

NIMESULIDE- β -CYCLODEXTRIN 400 MG
TABLETS AND GRANULES FOR ORAL SUSPENSION

1. NAME OF THE MEDICINAL PRODUCT

<TRADENAME>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet and tablet contains 400mg nimesulide- β -cyclodextrin, corresponding to 100mg nimesulide.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet: <Company-specific>Granules for oral suspension: <Company-specific>.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute pain.
Symptomatic treatment of painful osteoarthritis.
Primary dysmenorrhoea.

4.2 Posology and method of administration

<Nimesulide-containing medicinal products> should be used for the shortest possible duration, as required by the clinical situation.

Adults:

400mg nimesulide- β -cyclodextrin sachet and tablet (=100mg nimesulide) bid after meal.

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

Children (< 12 years): <Nimesulide containing medicinal products> are 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 <Nimesulide containing medicinal products> are contraindicated in case of severe renal impairment (creatinine clearance < 30ml/min) (see sections 4.3 and 5.2).

Hepatic impairment: the use of <Nimesulide containing medicinal products> is contraindicated in patients with hepatic impairment (see section 5.2).

4.3 Contraindications

Known hypersensitivity to nimesulide or to any of the excipients of the products.
History of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) in response to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.

History of hepatotoxic reactions to nimesulide
Active gastric or duodenal ulcer, a history of recurrent ulceration or gastrointestinal bleeding, cerebrovascular bleeding or other active bleeding or bleeding disorders.
Severe coagulation disorders.
Severe heart failure
Severe renal impairment.
Hepatic impairment.
Children under 12 years.
The third trimester of pregnancy and breastfeeding (see sections 4.6 and 5.3).

4.4 Special warnings and special precautions for use

The risk of undesirable effects may be reduced by using <Nimesulide- containing medicinal products> for the shortest possible duration.

Treatment should be discontinued if no benefit is seen.

Rarely <Nimesulide-containing medicinal products> have 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 <Nimesulide-containing medicinal products> (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.

Concomitant administration with known hepatotoxic drugs, and alcohol abuse must be avoided during treatment with <Nimesulide-containing medicinal products>, since either may increase the risk of hepatic reactions.

During therapy with <Nimesulide-containing medicinal products>, patients should be advised to refrain from other analgesics. Simultaneous use of different NSAIDs is not recommended.

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.

In patients with renal or cardiac impairment, caution is required since the use of <Nimesulide-containing medicinal products> may result in deterioration of renal function. In the event of deterioration, the treatment should be discontinued (see also section 4.5).

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including gastrointestinal haemorrhage and perforation, impaired renal, cardiac and hepatic function. Therefore, appropriate clinical monitoring is advisable.

As nimesulide can interfere with platelet function, it should be used with caution in patients with bleeding diathesis (see also section 4.3). However, <Nimesulide-containing medicinal products> is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis.

NSAIDs may mask the fever related to an underlying bacterial infection.

The use of <Nimesulide-containing medicinal products> 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 <Nimesulide-containing medicinal products> should be considered (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Patients receiving warfarin or similar anticoagulant agents or acetylsalicylic acid have an increased risk of bleeding complications, when treated with <Nimesulide-containing medicinal products>. 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.

Pharmacodynamic/pharmacokinetic interactions with diuretics

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 <Nimesulide containing medicinal products> requires caution in susceptible renal or cardiac patients, as described under section 4.4.

Pharmacokinetic interactions with other drugs:

Non-steroidal anti-inflammatory drugs have been reported to reduce the clearance of lithium, resulting in elevated plasma levels and lithium toxicity. If <Nimesulide containing medicinal products> 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 <Nimesulide containing medicinal products> 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 prostaglandines, prostaglandin synthetase inhibitors like nimesulide may increase the nephrotoxicity of cyclosporines.

Effects of other drugs on 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 Pregnancy and lactation

The use of <Nimesulide containing medicinal products> is contraindicated in the third trimester of pregnancy (see section 4.3).

Like other NSAIDs, <Nimesulide containing medicinal products> is not recommended in women attempting to conceive (see section 4.4). As with other NSAIDs known to inhibit prostaglandin synthesis, nimesulide may cause premature closure of the ductus arteriosus, pulmonary hypertension, oliguria, oligoamnios, increased risk of bleeding, uterine inertia and peripheral oedema. There have been isolated reports of renal failure in neonates born to women taking nimesulide in late pregnancy.

Studies in rabbits have shown an atypical reproductive toxicity (see section 5.3) and no adequate data from the use of nimesulide-containing medicinal products 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.

Lactation:

It is not known whether nimesulide is excreted in human milk. <Nimesulide containing medicinal products> are 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 <Nimesulide containing medicinal products> on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence after receiving <Nimesulide containing medicinal products> should refrain from driving or operating machines.

4.8 Undesirable effects

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.

<i>Blood disorders</i>	Rare	Anaemia* Eosinophilia*
	Very rare	Thrombocytopenia Pancytopenia Purpura
<i>Immune system disorders</i>	Rare	Hypersensitivity*
	Very rare	Anaphylaxis
<i>Metabolism and nutrition disorders</i>	Rare	Hyperkalaemia*
<i>Psychiatric disorders</i>	Rare	Anxiety* Nervousness* Nightmare*
<i>Nervous system disorders</i>	Uncommon	Dizziness*
	Very rare	Headache Somnolence Encephalopathy (Reye's syndrome)
<i>Eye disorders</i>	Rare	Vision blurred*
	Very rare	Visual disturbance
<i>Ear and labyrinth disorders</i>	Very rare	Vertigo
<i>Cardiac disorders</i>	Rare	Tachycardia*
<i>Vascular disorders</i>	Uncommon	Hypertension*
	Rare	Haemorrhage* Blood pressure fluctuation* Hot flushes*
<i>Respiratory disorders</i>	Uncommon	Dyspnoea*
	Very rare	Asthma Bronchospasm
<i>Gastrointestinal disorders</i>	Common	Diarrhoea* Nausea* Vomiting*
	Uncommon	Constipation* Flatulence* Gastritis*

	Very rare	Abdominal pain Dyspepsia Stomatitis Melaena Gastrointestinal bleeding Duodenal ulcer and perforation Gastric ulcer and perforation
<i>Hepato-biliary disorders (see section 4.4. "Special warnings and special precautions for use")</i>	Very rare	Hepatitis Fulminant hepatitis (including fatal cases) Jaundice Cholestasis
<i>Skin and subcutaneous tissue disorders</i>	Uncommon	Pruritus* Rash* Sweating increased*
	Rare	Erythema* Dermatitis*
	Very rare	Urticaria Angioneurotic oedema Face oedema Erythema multiforme Stevens Johnson syndrome Toxic epidermal necrolysis
<i>Renal and urinary disorders</i>	Rare	Dysuria* Haematuria* Urinary retention*
	Very rare	Renal failure Oliguria Interstitial nephritis
<i>General disorders</i>	Uncommon	Oedema*
	Rare	Malaise* Asthenia*
	Very rare	Hypothermia
<i>Investigations</i>	Common	Hepatic enzymes increased*

**frequency based on clinical trial*

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

Nimesulide is well absorbed when given by mouth. 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.

After single doses, nimesulide β -cyclodextrin 400 mg sachets were found bioequivalent to <Nimesulide containing medicinal products> 100 mg sachets, with respect to AUC and C_{max} parameters. Moreover t_{1/2} was nearly identical for both formulations, while the T_{max} was about 1.5 and 2.5 hrs. respectively for nimesulide β -cyclodextrin sachets and <Nimesulide containing medicinal products> sachets, showing a more rapid absorption of the former.

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_{1/2} 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 t_{1/2} 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

6.2 Incompatibilities

6.3 Shelf life

6.4 Special precautions for storage

6.5 Nature and contents of the container

6.6 Instructions for use/handling

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION /RENEWAL OF AUTHORISATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT

SUMMARY OF PRODUCT CHARACTERISTICS
NIMESULIDE 100 MG OR 200 MG SUPPOSITORIES

1. NAME OF THE MEDICINAL PRODUCT

<TRADENAME>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains 100mg or 200mg nimesulide.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Suppository: <Company-specific>.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute pain.
Symptomatic treatment of painful osteoarthritis.
Primary dysmenorrhoea.

4.2 Posology and method of administration

<Nimesulide-containing medicinal products> should be used for the shortest possible duration, as required by the clinical situation.

Adults:

100mg or 200mg nimesulide suppositories: 200mg twice daily

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

Children (< 12 years): <Nimesulide containing medicinal products> are 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 <Nimesulide containing medicinal products> are contraindicated in case of severe renal impairment (creatinine clearance < 30ml/min) (see sections 4.3 and 5.2).

Hepatic impairment: the use of <Nimesulide containing medicinal products> is contraindicated in patients with hepatic impairment (see section 5.2).

4.3 Contraindications

Known hypersensitivity to nimesulide or to any of the excipients of the products.
History of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) in response to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
History of hepatotoxic reactions to nimesulide
Active gastric or duodenal ulcer, a history of recurrent ulceration or gastrointestinal bleeding, cerebrovascular bleeding or other active bleeding or bleeding disorders.
Severe coagulation disorders.
Severe heart failure
Severe renal impairment.

Hepatic impairment.
Children under 12 years.
The third trimester of pregnancy and breastfeeding (see sections 4.6 and 5.3).

4.4 Special warnings and special precautions for use

The risk of undesirable effects may be reduced by using <Nimesulide-containing medicinal products> for the shortest possible duration.

Treatment should be discontinued if no benefit is seen.

Rarely <Nimesulide-containing medicinal products> have 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 <Nimesulide-containing medicinal products> (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.

Concomitant administration with known hepatotoxic drugs, and alcohol abuse must be avoided during treatment with <Nimesulide-containing medicinal products>, since they either increase the risk of hepatic reactions.

During therapy with <Nimesulide-containing medicinal products>, patients should be advised to refrain from other analgesics. Simultaneous use of different NSAIDs is not recommended.

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.

In patients with renal or cardiac impairment, caution is required since the use of <Nimesulide-containing medicinal products> may result in deterioration of renal function. In the event of deterioration, the treatment should be discontinued (see also section 4.5).

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including gastrointestinal haemorrhage and perforation, impaired renal, cardiac and hepatic function. Therefore, appropriate clinical monitoring is advisable.

As nimesulide can interfere with platelet function, it should be used with caution in patients with bleeding diathesis (see also section 4.3). However, <Nimesulide-containing medicinal products> is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis.

NSAIDs may mask the fever related to an underlying bacterial infection.

The use of <Nimesulide-containing medicinal products> 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 <Nimesulide-containing medicinal products> should be considered (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Patients receiving warfarin or similar anticoagulant agents or acetylsalicylic acid have an increased risk of bleeding complications, when treated with <Nimesulide-containing medicinal products>. 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.

Pharmacodynamic/pharmacokinetic interactions with diuretics

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 <Nimesulide containing medicinal products> requires caution in susceptible renal or cardiac patients, as described under section 4.4.

Pharmacokinetic interactions with other drugs:

Non-steroidal anti-inflammatory drugs have been reported to reduce the clearance of lithium, resulting in elevated plasma levels and lithium toxicity. If <Nimesulide containing medicinal products> 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 <Nimesulide containing medicinal products> 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 prostaglandines, prostaglandin synthetase inhibitors like nimesulide may increase the nephrotoxicity of cyclosporines.

Effects of other drugs on 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 Pregnancy and lactation

The use of <Nimesulide containing medicinal products> is contraindicated in the third trimester of pregnancy (see section 4.3).

Like other NSAIDs, <Nimesulide containing medicinal products> is not recommended in women attempting to conceive (see section 4.4).

As with other NSAIDs known to inhibit prostaglandin synthesis, nimesulide may cause premature closure of the ductus arteriosus, pulmonary hypertension, oliguria, oligoamnios, increased risk of bleeding, uterine inertia and peripheral oedema. There have been isolated reports of renal failure in neonates born to women taking nimesulide in late pregnancy.

Studies in rabbits have shown an atypical reproductive toxicity (see section 5.3) and no adequate data from the use of nimesulide-containing medicinal products 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.

Lactation:

It is not known whether nimesulide is excreted in human milk. <Nimesulide containing medicinal products> are 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 <Nimesulide containing medicinal products> on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence after receiving <Nimesulide containing medicinal products> should refrain from driving or operating machines.

4.8 Undesirable effects

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* Gastritis*
	Very rare	Abdominal pain Dyspepsia Stomatitis Melaena Gastrointestinal bleeding Duodenal ulcer and perforation Gastric ulcer and perforation

<i>Hepato-biliary disorders</i> (see section 4.4. "Special warnings and special precautions for use")	Very rare	Hepatitis Fulminant hepatitis (including fatal cases) Jaundice Cholestasis
<i>Skin and subcutaneous tissue disorders</i>	Uncommon	Pruritus* Rash* Sweating increased*
	Rare	Erythema* Dermatitis*
	Very rare	Urticaria Angioneurotic oedema Face oedema Erythema multiforme Stevens Johnson syndrome Toxic epidermal necrolysis
<i>Renal and urinary disorders</i>	Rare	Dysuria* Haematuria* Urinary retention*
	Very rare	Renal failure Oliguria Interstitial nephritis
<i>General disorders</i>	Uncommon	Oedema*
	Rare	Malaise* Asthenia*
	Very rare	Hypothermia
<i>Investigations</i>	Common	Hepatic enzymes increased*
*frequency based on clinical trial		

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

After a single administration of <Nimesulide containing medicinal products> 200 mg suppository, a peak plasma level of about 2 mg/l is reached in 4 hours, with mean AUC of 27 mg h/l. The corresponding values at the steady state were C_{max} about 3 mg/l; T_{max} = 4 hours and AUC of 25 mg h/l. Moreover, <Nimesulide containing medicinal products> 200 mg suppositories were found bioequivalent to <Nimesulide containing medicinal products> 100 mg tablets, despite a longer T_{max} and a reduced C_{max}.

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 t_{1/2} 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**
 - 6.2 Incompatibilities**
 - 6.3 Shelf life**
 - 6.4 Special precautions for storage**
 - 6.5 Nature and contents of the container**
 - 6.6 Instructions for use/handling**
- 7. MARKETING AUTHORISATION HOLDER**
- 8. MARKETING AUTHORISATION NUMBER**
- 9. DATE OF FIRST AUTHORISATION /RENEWAL OF AUTHORISATION**
- 10. DATE OF (PARTIAL) REVISION OF THE TEXT**

SUMMARY OF PRODUCT CHARACTERISTICS

NIMESULIDE 3% GEL / CREAM

1. NAME OF THE MEDICINAL PRODUCT

<TRADENAME>

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nimesulide 3% gel / cream contains 3% w/w nimesulide (1 g of gel / cream contains 30 mg of nimesulide)

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Gel : <Company-specific>

Cream : <Company-specific>

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic relief of pain associated with sprains and acute traumatic tendinitis.

4.2 Posology and method of administration

Adults: Nimesulide 3% gel / cream (usually 3 g, corresponding to a line 6-7 cm long) should be applied in a thin layer to the affected area 2-3 times daily and massaged until it is completely absorbed.

Duration of treatment: 7 – 15 days.

Children under 12 years: Nimesulide 3% gel / cream has not been studied in children. Therefore, safety and efficacy have not been established and the product should not be used in children (see section 4.3).

4.3 Contraindications

Known hypersensitivity to nimesulide or to any other excipients in the gel / cream.

Use in patients in whom aspirin, or other medicinal products inhibiting prostaglandin synthesis, induced allergic reactions such as rhinitis, urticaria or bronchospasm.

Use on broken or denuded skin or in the presence of local infection.

Simultaneous use with other topical creams.

Use in children under 12 years.

4.4 Special warnings and special precautions for use

Nimesulide 3% gel / cream should not be applied to skin wounds or open injuries.

Nimesulide 3% gel / cream should not be allowed to come into contact with the eyes or mucous membranes; in case of accidental contact, wash immediately with water.

The product should never be taken by mouth. Hands should be washed after applying the product.

Nimesulide 3% gel / cream should not be used with occlusive dressings.

Nimesulide 3% gel / cream is not recommended for use in children under 12 years (see section 4.3).

Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration.

Patients with gastro-intestinal bleeding, active or suspected peptic ulcer, severe renal or hepatic dysfunction, severe coagulation disorders or severe/non controlled heart failure should be treated with caution.

Since nimesulide gel 3% / cream has not been studied in hypersensitive subjects, particular caution should be used when treating patients with known hypersensitivity to other NSAIDs. The possibility of developing hypersensitivity in the course of therapy cannot be excluded.

Since with other topical NSAIDs burning sensation and exceptionally photodermatitis can occur, care should be taken during treatment with Nimesulide 3% gel / cream.

To reduce the risk of photosensitivity, patients should be warned against exposure to direct and solarium sunlight.

If symptoms persist or the condition is aggravated medical advice should be sought.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of Nimesulide 3% gel / cream with other medicinal products are known or to be expected via the topical route.

4.6 Pregnancy and lactation

There are no data relevant to the topical use of <nimesulide containing medicinal product> in pregnant women or during breastfeeding. Therefore, nimesulide 3% gel / cream should not be used during pregnancy or lactation unless clearly necessary.

4.7 Effects on ability to drive and use machines

No studies on the effect of nimesulide 3% gel / cream on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The following side effects listing is based on reports from clinical studies, in a limited numbers of patients, where mild local reactions have been reported. The reporting rates are 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.

Skin and subcutaneous tissue disorders (see also section 4.4)	Common	Itching Erythema
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4.9 Overdose

Intoxication with nimesulide as a result of topical application of Nimesulide 3% gel or cream is not to be expected since the highest plasma levels of nimesulide following application of Nimesulide 3% gel / cream are far below those found following systemic administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: M02AA.

Non-steroidal anti-inflammatory drug (NSAID) for topical use.

Nimesulide is an inhibitor of the prostaglandin synthesis enzyme cyclo-oxygenase.

Cyclo-oxygenase produces prostaglandins, some of them being implicated in the development and maintenance of inflammation.

5.2 Pharmacokinetic properties

When Nimesulide 3% is applied topically, plasma concentrations of nimesulide are very low in comparison with those achieved following oral intake. After a single application of 200mg of nimesulide, in the gel form, the highest plasma level of 9.77 ng/ml was noted after 24 hours. No trace of the main metabolite 4-hydroxy-nimesulide, was detected. At steady-state (day 8) peak plasma concentrations were higher (37.25 ± 13.25 ng/ml, but almost 100 times lower than those measured following repeated oral administration.

5.3 Preclinical safety data

The local tolerance and the irritation and sensitisation potential of Nimesulide 3% have been tested in several recognised animal models. The results of these studies indicate that Nimesulide 3% is well tolerated.

Preclinical data for systemically administered nimesulide 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

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