

# Seractil 400mg Film-Coated Tablets

Summary of Product Characteristics Updated 30-Sep-2005 | Genus Pharmaceuticals

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

## 1. Name of the medicinal product

Seractil ▼ 400 mg film-coated tablets

## 2. Qualitative and quantitative composition

Each film-coated tablet contains 400 mg of dexibuprofen. For excipients, see 6.1.

## 3. Pharmaceutical form

Film-coated tablet

White, oblong, both-sided scored film-coated tablet.

## 4. Clinical particulars

### 4.1 Therapeutic indications

Symptomatic treatment for the relief of pain and inflammation associated with osteoarthritis.

Acute symptomatic treatment of pain during menstrual bleeding (primary dysmenorrhoea).

Symptomatic treatment of other forms of mild to moderate pain, such as muscular-skeletal pain or dental pain.

### 4.2 Posology and method of administration

The dosage should be adjusted to the severity of the disorder and the complaints of the patient. During chronic administration, the dosage should be adjusted to the lowest maintenance dose that provides adequate control of symptoms.

For individual dosage film-coated tablets with 200, 300 and 400 mg dexibuprofen are available.

The recommended dosage is 600 to 900 mg dexibuprofen daily, divided in up to three single doses.

For the treatment of mild to moderate pain, initially single doses of 200 mg dexibuprofen and daily doses of 600 mg dexibuprofen are recommended.

The maximum single dose is 400 mg dexibuprofen.

The dose may be temporarily increased up to 1200 mg dexibuprofen per day in patients with acute conditions or exacerbations. The maximum daily dose is 1200 mg.

For dysmenorrhoea a daily dose of 600 to 900 mg dexibuprofen, divided in up to three single doses, is recommended. The maximum single dose is 300 mg, the maximum daily dose is 900 mg.

Dexibuprofen has not been studied in children and adolescents (< 18 years): Safety and efficacy have not been established and therefore it is not recommended in these age groups.

In elderly patients it is recommended to start the therapy at the lower end of the dosage range. The dosage may be increased to that recommended for general population only after good general tolerance has been ascertained.

Hepatic dysfunction: Patients with mild to moderate hepatic dysfunction should start therapy at reduced doses and be closely monitored. Dexibuprofen should not be used in patients with severe hepatic dysfunction (see 4.3. Contraindications).

Renal dysfunction: The initial dosage should be reduced in patients with mild to moderate impaired renal function. Dexibuprofen should not be used in patients with severe renal dysfunction (see 4.3. Contraindications).

The film coated tablets can be taken with or without a meal (see 5.2.). In general NSAIDs (non-steroidal anti-inflammatory drugs) are preferably taken with food to reduce gastrointestinal irritation, particularly during chronic use. However, a later onset of action in some patients may be anticipated when the tablets are taken with or directly after a meal.

The score in the 200 and 400 mg tablets makes it possible to divide the tablets before administration so as to assist with

swallowing.

Dividing the tablets will not provide an exact "half" dose.

### 4.3 Contraindications

Dexibuprofen must not be administered in the following cases:

- Patients previously sensitive to dexibuprofen, to any other NSAID, or to any of the excipients of the product.
- Patients in whom substances with a similar action (e.g. aspirin or other NSAIDs) precipitate attacks of asthma, bronchospasm, acute rhinitis, or cause nasal polyps, urticaria or angioneurotic oedema.
- Patients with active or suspected gastrointestinal ulcer or history of recurrent gastrointestinal ulcer.
- Patients who have gastrointestinal bleeding or other active bleedings or bleeding disorders.
- Patients with active Crohn's disease or active ulcerative colitis.
- Patients with severe heart failure.
- Patients with severe renal dysfunction (GFR < 30ml/min).
- Patients with severely impaired hepatic function.
- Patients with haemorrhagic diathesis and other coagulation disorders, or patients receiving anticoagulant therapy.
- From the beginning of 6<sup>th</sup> month of pregnancy (see 4.6).

### 4.4 Special warnings and precautions for use

Care is recommended in conditions that predispose patients to the gastrointestinal adverse effects of NSAIDs such as dexibuprofen, including existing gastrointestinal disorders, previous gastric or duodenal ulcer, ulcerative colitis, Crohn's disease and alcoholism.

These patients should be closely monitored for digestive disturbances, especially gastrointestinal bleeding, when taking dexibuprofen or any other NSAID.

Gastrointestinal bleeding or ulceration/perforation have in general more serious consequences in the elderly. They can occur at any time during treatment with or without warning symptoms or a previous history of serious gastrointestinal events.

In the rare instances where gastrointestinal bleeding or ulceration occurs in patients receiving dexibuprofen, treatment should be immediately discontinued (see 4.3. Contraindications).

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

In the treatment of patients with heart failure, hypertension, renal or hepatic disease, especially during concomitant diuretic treatment, the risk of fluid retention and a deterioration in renal function must be taken into account. If used in these patients, the dose of dexibuprofen should be kept as low as possible and renal function should be regularly monitored.

Caution must be exercised in the treatment of elderly patients, who generally have a greater tendency to experience side effects to NSAIDs.

Dexibuprofen should only be given with care to patients with systemic lupus erythematosus and mixed connective tissue disease, because such patients may be predisposed to NSAID-induced CNS and renal side effects.

Caution is required in patients suffering from, or with a previous history of, bronchial asthma since NSAIDs can cause bronchospasm in such patients (see 4.3 Contraindications).

NSAIDs may mask the symptoms of infections.

As with all NSAIDs, dexibuprofen can increase plasma urea nitrogen and creatinine. As with other NSAIDs, dexibuprofen can be associated with adverse effects on the renal system, which can lead to glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome and acute renal failure (see 4.2. Posology, 4.3. Contraindications and 4.5 Interactions).

As with other NSAIDs, dexibuprofen can cause transient small increases in some liver parameters, and also significant increases in SGOT and SGPT. In case of a relevant increase in such parameters, therapy must be discontinued (see 4.2. Posology and 4.3. Contraindications).

In common with other NSAIDs dexibuprofen may reversibly inhibit platelet aggregation and function and prolong bleeding time. Caution should be exercised when dexibuprofen is given concurrently with oral anticoagulants (see section 4.5).

Patients receiving long-term treatment with dexibuprofen should be monitored as a precautionary measure (renal, hepatic functions and haematologic function/blood counts).

During long-term, high dose, off-label treatment with analgesic drugs, headaches can occur which must not be treated with higher doses of the medicinal product.

In general the habitual use of analgesics, especially the combination of different analgesic drug substances, can lead to lasting renal lesions with the risk of renal failure (analgesic nephropathy). Thus combinations with racemic ibuprofen or other NSAIDs (including OTC products) should be avoided.

The use of dexibuprofen, as with any other drug known to inhibit cyclooxygenase / prostaglandin synthesis, may impair fertility reversibly and is not recommended in women attempting to conceive. In women who have difficulty conceiving or who are undergoing investigation of infertility, withdrawal of Seractil should be considered.

Data of preclinical studies indicate that inhibition of platelet aggregation by low-dose acetylsalicylic acid may be impaired if ibuprofen is administered concurrently;

this interaction could reduce the cardiovascular-protective effect. Therefore if concomitant administration of low-dose acetylsalicylic acid is indicated special precaution is required if duration of treatment exceeds short term use.

#### 4.5 Interaction with other medicinal products and other forms of interaction

The information in this section is based upon previous experience with racemic ibuprofen and other NSAIDs.

In general, NSAIDs should be used with caution with other drugs that can increase the risk of gastrointestinal ulceration or gastrointestinal bleeding or renal impairment.

##### **Concomitant use not recommended:**

Anticoagulants: The effects of anticoagulants on bleeding time can be potentiated by NSAIDs. If concomitant treatment can not be avoided blood coagulation tests (INR, bleeding time) should be performed during the initiation of dexibuprofen treatment and the dosage of the anticoagulant should be adjusted if necessary (see section 4.4).

Methotrexate used at doses of 15 mg/week or more: If NSAIDs and methotrexate are given within 24 hours of each other plasma levels of methotrexate may increase, via a reduction in its renal clearance thus increasing the potential for methotrexate toxicity. Therefore, in patients receiving high-dose treatment with methotrexate, the concomitant use of dexibuprofen is not recommended (see section 4.4).

Lithium: NSAIDs can increase the plasma levels of lithium, by reducing its renal clearance. The combination is not recommended (see section 4.4). Frequent lithium monitoring should be performed. The possibility of reducing the dose of lithium should be considered.

Other NSAIDs and salicylates ( acetylsalicylic acid at doses above those used for anti-thrombotic treatment, approximately 100 mg/day ): The concomitant use with other NSAIDs should be avoided, since simultaneous administration of different NSAIDs can increase the risk of gastrointestinal ulceration and haemorrhage.

##### **Precautions:**

Acetylsalicylic acid: Concomitant administration of ibuprofen may impair inhibition of platelet aggregation by low-dose acetylsalicylic acid.

Antihypertensives : NSAIDs may reduce the efficacy of beta-blockers, possibly due to inhibition of the formation of vasodilatory prostaglandins.

The concomitant use of NSAIDs and ACE inhibitors or angiotensin-II receptor antagonists may be associated with an increased risk of acute renal failure, especially in patients with pre-existing impairment of renal function. When given to the elderly and/or dehydrated patients, such a combination can lead to acute renal failure by acting directly on

glomerular filtration. At the beginning of the treatment, a careful monitoring of renal function is recommended.

Furthermore, chronic administration of NSAIDs can theoretically reduce the antihypertensive effect of angiotensin-II receptor antagonists, as reported with ACE inhibitors. Therefore, caution is required when using such a combination and at the start of treatment, renal function should be carefully monitored (and patients should be encouraged to maintain adequate fluid intake).

Cyclosporin, tacrolimus: Concomitant administration with NSAIDs may increase the risk of nephrotoxicity on account of reduced synthesis of prostaglandins in the kidney. During combination treatment renal function must be closely monitored, especially in the elderly.

Corticosteroids: The risk of gastrointestinal ulceration may be increased by the concomitant administration of NSAIDs and corticosteroids.

Digoxin : NSAIDs can increase the plasma levels of digoxin and increase the risk of digoxin toxicity.

Methotrexate used at doses lower than 15 mg/week : Ibuprofen has been reported to increase methotrexate levels. If dexibuprofen is used in combination with low doses of methotrexate, then the patient's blood count should be monitored carefully, particularly during the first weeks of coadministration. An increased surveillance is required in the presence of even mildly impaired renal function, notably in the elderly, and renal function should be monitored to anticipate any reductions in the clearance of methotrexate.

Phenytoin:Ibuprofen may displace phenytoin from protein-binding sites, possibly leading to increased phenytoin serum levels and toxicity. Although clinical evidence for this interaction is limited, phenytoin dosage adjustment, based on monitoring of plasma concentrations and/or observed signs of toxicity, is recommended.

Thiazides, thiazide-related substances, loop diuretics and potassium-sparing diuretics: Concurrent use of an NSAID and a diuretic may increase the risk of renal failure secondary to a reduction in renal blood flow.

#### *Drugs increasing potassium plasma levels:*

As with other NSAIDs, concomitant treatment with drugs increasing potassium plasma levels, like potassium-sparing diuretics, ACE inhibitors, angiotensin-II receptors antagonists, immunosuppressants like cyclosporin or tacrolimus, trimethoprim, heparins, etc... may be associated with increased serum potassium levels; hence serum potassium levels should be monitored.

Thrombolytics, ticlopidine and antiplatelet agents: Dexibuprofen inhibits platelet aggregation via inhibition of platelet cyclooxygenase. Therefore, caution is required when dexibuprofen is combined with thrombolytics, ticlopidine and other antiplatelet agents, because of the risk of increased antiplatelet effect.

## 4.6. Pregnancy and lactation

### *Pregnancy:*

For dexibuprofen, no clinical data on exposed pregnancies are available. Animal studies with ibuprofen and other NSAIDs have shown reproductive toxicity (see 5.3 Preclinical Safety Data).

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development, and as the consequences of inhibiting the synthesis of prostaglandins are not fully known, dexibuprofen, like other drugs of this class, should only be administered in the first 5 months of pregnancy if clearly needed, in the lowest effective dose and as short as possible.

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

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension),
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis,

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time,
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Therefore, from the beginning of the 6<sup>th</sup> month of pregnancy onward dexibuprofen is contraindicated.

The use of dexibuprofen, as with any drug substance known to inhibit cyclooxygenase / prostaglandin synthesis is not recommended in women attempting to conceive (see 4.4).

### Lactation:

Ibuprofen is slightly excreted in human milk. Breast-feeding is possible with dexibuprofen if dosage is low and the treatment period is short.

#### 4.7 Effects on ability to drive and use machines

During treatment with dexibuprofen the patient's reaction capacity may be reduced when dizziness or fatigue appear as side effects. This should be taken into consideration when increased alertness is required, e.g. when driving or operating machinery. For a single or short term use of Dexibuprofen no special precautions are necessary.

#### 4.8 Undesirable effects

Clinical experience has shown that the risk of undesirable effects induced by dexibuprofen is comparable to that of racemic ibuprofen. The most common adverse events are gastrointestinal in nature.

It should be noted that the adverse events listed below include those reported predominantly for racemic ibuprofen, even though in some cases the adverse event has either not yet been observed with dexibuprofen or has not yet been reported in the frequency mentioned.

##### Gastrointestinal :

Very common (>1/10): Dyspepsia, diarrhoea.

Common (>1/100, <1/10): Nausea, vomiting, abdominal pain.

Uncommon (>1/1,000, <1/100): Gastrointestinal ulcers and bleeding, ulcerative stomatitis.

Rare (>1/10,000, <1/1,000): Gastrointestinal perforation, flatulence, constipation, esophagitis, esophageal strictures. Exacerbation of diverticular disease, unspecific haemorrhagic colitis, colitis ulcerosa or Crohn's disease.

If gastrointestinal blood loss occurs, this may cause anaemia and haematemesis.

##### Skin and hypersensitivity reaction:

Common: Rash.

Uncommon: Urticaria, pruritus, purpura (including allergic purpura), angioedema, rhinitis, bronchospasm.

Rare: Anaphylactic reaction

Very rare (<1/10,000): Erythema multiforme, epidermal necrolysis, systemic lupus erythematosus, alopecia, photosensitivity reactions, severe skin reactions like Stevens-Johnson-Syndrome, acute toxic epidermal necrolysis (Lyell-Syndrome) and allergic vasculitis.

Generalized hypersensitivity reactions have not yet been reported with dexibuprofen but their occurrence cannot be excluded considering the clinical experience with racemic ibuprofen. The symptoms may include fever with rash, abdominal pain, headache, nausea and vomiting, signs of liver injury and even aseptic meningitis. In the majority of cases in which aseptic meningitis has been reported with ibuprofen, some form of underlying auto-immune disease (such as systemic lupus erythematosus or other collagen diseases) was present as a risk factor. In case of a severe generalized hypersensitivity reaction swelling of face, tongue and larynx, bronchospasm, asthma, tachycardia, hypotension and shock can occur.

##### Central nervous system:

Common: Fatigue or drowsiness, headache, dizziness, vertigo.

Uncommon: Insomnia, anxiety, restlessness, visual disturbances, tinnitus.

Rare: Psychotic reaction, agitation, irritability, depression, confusion or disorientation, reversible toxic amblyopia, impaired hearing.

Very rare: Aseptic meningitis (see hypersensitivity reactions).

##### Haematological:

Bleeding time may be prolonged. Rare cases of blood disorders include: Thrombocytopenia, leucopenia, granulocytopenia, pancytopenia, agranulocytosis, aplastic anemia or haemolytic anaemia.

##### Cardiovascular:

Peripheral oedema has been reported in association with dexibuprofen treatment.

Patients with hypertension or renal impairment seem to be predisposed to fluid retention.

Hypertension or cardiac failure (especially in the elderly) may occur.

#### Renal:

According to the experience with NSAIDs in general, interstitial nephritis, nephrotic syndrome or renal failure cannot be excluded.

#### Hepatic:

Rare cases of abnormal liver function, hepatitis and jaundice have been observed with racemic ibuprofen.

#### Others:

In very rare cases infection related inflammation may be aggravated.

### 4.9 Overdose

Dexibuprofen has a low acute toxicity and patients have survived after single doses as high as 54 g of racemic ibuprofen. Most overdoses have been asymptomatic. There is a risk of symptoms at doses >80 - 100 mg/kg racemic ibuprofen.

The onset of symptoms usually occurs within 4 hours. Mild symptoms are most common, including abdominal pain, nausea, vomiting, lethargy, drowsiness, headache, nystagmus, tinnitus and ataxia. Rarely, moderate or severe symptoms include gastrointestinal bleeding, hypotension, hypothermia, metabolic acidosis, seizures, impaired kidney function, coma, adult respiratory distress syndrome and transient episodes of apnea (in very young children following large ingestions).

Treatment is symptomatic, and there is no specific antidote. Amounts not likely to produce symptoms (less than 50 mg/kg dexibuprofen) may be diluted with water to minimize gastrointestinal upset. In case of ingestion of a significant amount, activated charcoal should be administered.

Emptying of the stomach by emesis may only be considered if the procedure can be undertaken within 60 minutes of ingestion. Gastric lavage should not be considered unless a patient has ingested a potentially life-threatening amount of the drug and the procedure can be undertaken within 60 minutes of ingestion. Forced diuresis, hemodialysis or hemoperfusion are unlikely to be of assistance because dexibuprofen is strongly bound to plasma proteins.

## 5. Pharmacological properties

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, non-steroids, propionic acid derivatives.

ATC code: M01AE14

### 5.1 Pharmacodynamic properties

Dexibuprofen (= S(+)-ibuprofen) is considered to be the pharmacologically active enantiomer of racemic ibuprofen. Racemic ibuprofen is a non-steroidal substance with antiinflammatory and analgesic effects. Its mechanism of action is thought to be due to inhibition of prostaglandin synthesis. Bridging studies in order to compare the efficacy of racemic ibuprofen and dexibuprofen in osteoarthritis over a treatment period of 15 days and in dysmenorrhea, including symptoms of pain, have demonstrated at least non-inferiority of dexibuprofen versus racemic ibuprofen at the recommended dosage.

### 5.2 Pharmacokinetic properties

Dexibuprofen is absorbed primarily from the small intestine. After metabolic transformation in the liver (hydroxylation, carboxylation), the pharmacologically inactive metabolites are completely excreted, mainly by the kidneys (90%), but also in the bile. The elimination half-life is 1.8 – 3.5 hours; the plasma protein binding is about 99 %. Maximum plasma levels are reached about 2 hours after oral administration.

The administration of dexibuprofen with a meal delays the time to reach maximum concentrations (from 2.1 hours after fasting conditions to 2.8 hours after non-fasting conditions) and decreases the maximum plasma concentrations (from 20.6 to 18.1 µg/ml, which is of no clinical relevance), but has no effect on the extent of absorption.

### 5.3 Preclinical safety data

Bridging studies on single and repeated dose toxicity, reproduction toxicity and mutagenicity have shown that the toxicological profile of dexibuprofen is comparable to that of racemic ibuprofen.

Racemic ibuprofen inhibited ovulation in the rabbit and impaired implantation in different animal species (rabbit, rat, mouse). Administration of prostaglandin synthesis inhibitors including ibuprofen (mostly in doses higher than used therapeutically) to pregnant animals has been shown to result in increased pre- and postimplantation loss, embryo-fetal lethality and increased incidences of malformations.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Tablet core: Hypromellose, microcrystalline cellulose, carmellose calcium, colloidal anhydrous silica, talc.

Film-coating material: Hypromellose, titanium dioxide (E171), glycerol triacetate, talc, macrogol 6000.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years (PVC/PVDC/aluminium blisters)

18 months (PE jars)

### 6.4 Special precautions for storage

Do not store above 25 °C.

### 6.5 Nature and contents of container

10, 20, 30, 50, 60, 90, 100, 100x1 and 500x1 film-coated tablets in PVC/PVDC/aluminium blisters.

150 film-coated tablets in PE jars with dosing hole and hinged closure.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. Marketing authorisation holder

Gebro Pharma GmbH, A-6391 Fieberbrunn

Austria

## 8. Marketing authorisation number(s)

PL 04536/0007

## 9. Date of first authorisation/renewal of the authorisation

31 October 2000

## 10. Date of revision of the text

April 2004

## 11. Legal category

POM

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