

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Betaren 100 S.R.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Diclofenac sodium 100 mg

Excipient with known effect:

Each tablet contains approximately 111.5 mg sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Slow release tablets

Pink, round, biconvex, film coated tablets, with an embossment "DICL100" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis, osteoarthritis, low back pain and other acute musculoskeletal disorders such as peri-arthritis, tendinitis, tenosynovitis, bursitis, sprains, strains and dislocation, ankylosing spondylitis and acute gout.

Control of pain and inflammation in orthopedic, dental, and other minor surgery.

4.2 Posology and method of administration

As a general recommendation, the dose should be given for the shortest possible duration.

Because of their dosage strength, Betaren is not suitable for children and adolescents.

The tablets should be swallowed whole with liquid, preferably with meals and must not be divided or chewed.

Generally 1 tablet daily is recommended. If gastrointestinal upset occurs, the dose may be taken with food, milk or antacids.

Where the symptoms are most pronounced during the night or in the morning, Betaren should preferably be taken in the evening.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active, gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy.

- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Last trimester of pregnancy (see section 4.6 Fertility, pregnancy and lactation).
- Hepatic failure
- Renal failure
- Established congestive heart failure (NYHA-II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticarial or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.

4.4 Special warnings and precautions for use

General

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 Posology and method of administration and GI and cardiovascular risks below).

The concomitant use of diclofenac sodium tablets with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

As with other nonsteroidal anti-inflammatory drugs, including diclofenac, allergic reactions, including anaphylactic/anaphylactoid reactions can also occur without earlier exposure to the drug (see section 4.8 Undesirable effects). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac.

Like other NSAIDs, diclofenac may mask the signs and symptoms of an infection due to its pharmacodynamic properties.

Gastrointestinal effects

Gastrointestinal bleeding (haematemesis, melaena), ulceration or perforation, which can be fatal has been reported with all NSAIDs including diclofenac, and may occur at any time during treatment, with or without warning symptoms or a previous history of serious GI events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the drug should be withdrawn.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.8 Undesirable effects). The risk of GI bleeding, ulceration or perforation is higher with increasing

NSAID doses including diclofenac and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation.

The elderly have increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low dose acetylsalicylic acid (ASA/aspirin or medicinal products likely to increase gastrointestinal risk (see section 4.5 Interaction with other medicinal products and other forms of interaction)).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding).

Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors (SSRIs) or anti-platelet agents such as acetylsalicylic acid (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Close medical surveillance and caution should be exercised in patients with ulcerative colitis or with Crohn's disease as these conditions may be exacerbated (see section 4.8 Undesirable effects).

NSAIDs, including diclofenac, may be associated with increased risk of gastrointestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.

Hepatic effects

Close medical surveillance is required when prescribing diclofenac to patients with impairment of hepatic function as their condition may be exacerbated.

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), diclofenac should be discontinued.

Hepatitis may occur with diclofenac without prodromal symptoms.

Caution is called for when using diclofenac in patients with hepatic porphyria, since it may trigger an attack.

Renal effects

As fluid retention and oedema have been reported in association with NSAIDs therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see section 4.3 Contraindications). Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation therapy is usually followed by recovery to the pre-treatment state.

Skin effects

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis and generalised bullous fixed drug eruption, have been reported very rarely in association with the use of diclofenac (see section 4.8 Undesirable effects). Patients appear to be at the 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. Diclofenac sodium tablets should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

SLE and mixed connective tissue disease

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

Cardiovascular and cerebrovascular effects

Patients with congestive heart failure (NYHA-I) or patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Appropriate monitoring and advice are required for patients with a history of hypertension and congestive heart failure (NYHA-I) as fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac.

Clinical trial and epidemiological data consistently point towards increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment.

Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.

Haematological effects

During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Diclofenac may reversibly inhibit platelet aggregation (see anticoagulants in section 4.5 Interaction with other medicinal products and other forms of interactions). Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

Pre-existing asthma

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics - asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for

emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

Female fertility

The use of Diclofenac may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Diclofenac should be considered (see section 4.6 Fertility, pregnancy and lactation).

Excipient(s) of known effect

Sucrose

This medicine contains sucrose. Patients with rare hereditary problems of the fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.

Lithium: If used concomitantly, diclofenac may increase plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and Anti-hypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics and antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity (see section 4.4 Special warnings and precautions for use).

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4 Special warnings and precautions for use).

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4 Special warnings and precautions for use). Although clinical investigations do not appear to indicate that diclofenac has an influence on the effect of anticoagulants, there are reports of an

increased risk of haemorrhage in patients receiving diclofenac and anticoagulant concomitantly (see section 4.4 Special warnings and precautions for use). Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Other NSAIDs including cyclo-oxygenase-2 selective inhibitors and corticosteroids:

Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs (see section 4.4 Special warnings and precautions for use).

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of SSRI's may increase the risk of gastrointestinal bleeding (see section 4.4 Special warnings and precautions for use).

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

Cases of serious toxicity have been reported when methotrexate and NSAIDs, including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

Ciclosporin: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostaglandin effects of both NSAID and calcineurin inhibitors.

Quinolone antibacterials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

Cardiac glycosides: Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Potent CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and / or cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1% up to approximately 1.5 %.

The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has shown to result in increased pre- and post-implantation loss and embryo-foetal lethality.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during organogenetic period.

From the 20th week of pregnancy onward, diclofenac use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, diclofenac should not be given unless clearly necessary. If diclofenac is used by a woman attempting to conceive, or during the first or second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to diclofenac for several days from gestational week 20 onward. Diclofenac should be discontinued if oligohydramnios or ductus arteriosus constriction is found.

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

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

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

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, diclofenac is contraindicated during the third trimester of pregnancy.

Breast-feeding

Like other NSAIDs, diclofenac passes into breast milk in small amounts. Therefore, diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant (see section 5.2 Pharmacokinetic properties).

Fertility

As with other NSAIDs, the use of diclofenac may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac should be considered.

See section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

Patients who experience visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances, drowsiness or fatigue while taking NSAIDs should refrain from driving or operating machinery.

4.8 Undesirable effects

Adverse reactions are ranked under the heading of frequency, the most frequent first, using the following convention: very common ($>1/10$); common ($\geq 1/100$, $<1/10$); uncommon ($\geq 1/1,000$, $<1/100$); rare ($\geq 1/10,000$, $<1/1,000$); very rare ($<1/10,000$); Not known: cannot be estimated from available data.

The following undesirable effects include those reported with other short-term or long-term use.

Table 1

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leucopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.
Immune system disorders	
Rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare	Angioneurotic oedema (including face oedema).
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common	Headache, dizziness.
Rare	Somnolence, tiredness.
Very rare	Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.
Not known	Confusion, hallucinations, disturbances of sensation, malaise.
Eye disorders	
Very rare	Visual disturbance, vision blurred, diplopia.
Not known	Optic neuritis.
Ear and labyrinth disorders	
Common	Vertigo.
Very rare	Tinnitus, hearing impaired.
Cardiac disorders	
Uncommon*	Myocardial infarction, cardiac failure, palpitations, chest pain.

Not known	Kounis syndrome.
Vascular disorders	
Very rare	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare	Asthma (including dyspnoea).
Very rare	Pneumonitis.
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly).
Very rare	Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.
Not known	Ischaemic colitis.
Hepatobiliary disorders	
Common	Transaminases increased.
Rare	Hepatitis, jaundice, liver disorder.
Very rare	Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common	Rash.
Rare	Urticaria.
Very rare	Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.
Not known	Fixed drug eruption, generalised bullous fixed drug eruption.
Renal and urinary disorders	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
Reproductive system and breast disorders	
Very rare	Impotence.
General disorders and administration site conditions	
Rare	Oedema.

** The frequency reflects data from long-term treatment with a high dose (150mg/day).*

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150 mg daily) and in long term treatment (see sections 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use).

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. Any suspected adverse events should be reported to the Ministry of Health

according to the National Regulation by using an online form
<https://sideeffects.health.gov.il>

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac over dosage. Over dosage can cause symptoms such as headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting or convulsions. In the case of significant poisoning acute renal failure and liver damage are possible.

Therapeutic measure

Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to high protein binding and extensive metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life threatening overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Acetic acid derivatives and related substances,
ATC code: M01AB05

Mechanism of action:

Diclofenac sodium is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase).

Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

5.2 Pharmacokinetic properties

After ingestion of the diclofenac slow release tablet, the active principle is slowly released into the gastrointestinal contents. Once released from the tablet, diclofenac is rapidly absorbed from the gastrointestinal tract but is subject to first-pass metabolism. Peak plasma concentrations occur about 4.5 hours after administration of the slow release tablets when taken with a meal. Food and antacids decrease the rate but not the extent of absorption of diclofenac. The systemic availability of diclofenac from the SR formulations is on average 82% of that achieved with the same dose of enteric-coated tablets (possibly due to release rate dependent first-pass metabolism). The active substance is 99.7% bound to plasma proteins, mainly albumin.

Diclofenac enters the synovial fluid and peak synovial fluid concentrations at steady state exceed plasma concentrations. Furthermore, elimination from the synovial fluid is slower than from plasma. Diclofenac and its metabolites cross the placenta and traces of diclofenac have been found in the milk of lactating women. The half-life for

the terminal elimination phase is 3 hours. Approximately 60% of the administered dose is excreted via the kidneys in the form of metabolites and less than 1% in unchanged form. About 30% of the dose is excreted via the bile in metabolised form. In patients with impaired renal function, accumulation of diclofenac sodium has not been reported. However, half-life of diclofenac may be prolonged in patients with severe renal impairment.

Five Diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy-Diclofenac. The major Diclofenac metabolite, 4'-hydroxy-Diclofenac, has very weak pharmacologic activity. The formation of 4'-hydroxy-Diclofenac is primarily mediated by CYP2C9. Both Diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CYP2C8 may also play a role in Diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy- and 3'-hydroxy-Diclofenac. In patients with renal dysfunction, peak concentrations of metabolites 4'-hydroxy- and 5-hydroxy-Diclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects.

5.3 Preclinical safety data

Relevant information on the safety of Betaren 100 S.R. is included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Compressible sugar, cetostearyl alcohol, talc, povidone, silica colloidal anhydrous, hypromellose, magnesium stearate, titanium dioxide (E171), sucrose, macrogol 400, copovidone, gum acacia, carnauba wax, iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Blister.

Pack sizes: 10, 20 or 30 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Dexcel Ltd., 1 Dexcel Street, Or Akiva 3060000, Israel

8 MARKETING AUTHORISATION NUMBER

015-73-24619-00

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