SUMMARY OF PRODUCT CHARACTERISTICS

Swiss Relief Dual Release, 75 mg capsules

1. NAME OF THE MEDICINAL PRODUCT

Swiss Relief Dual Release
75 mg capsule
Diclofenac sodium

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule, hard, contains 75 mg diclofenac sodium (25 mg diclofenac sodium in gastro-resistant form, 50 mg diclofenac sodium in prolonged-release form).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, hard.
Size 2 hard gelatine capsule with light blue cap and transparent body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

As a non-steroidal anti-inflammatory analgesic in symptomatic management of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, acute musculo-skeletal disorders such as periarthritis, tendinitis, tensynovitis, bursitis, sprains, strains and dislocations, relief of pain in fractures, low back pain, acute gout, psoriatic arthropathy.
In the management of pain and inflammation associated with orthopaedic, dental and minor surgery.

4.2 Posology and method of administration

Posology:
Diclofenac is dosed in relation to the severity of the condition. The recommended dose range for adults is between 50 and 150 mg diclofenac sodium per day.

Age:	Single dose: Number of Swiss Relief Dual Release capsules	Total daily dose: Number of Swiss Relief Dual Release capsules
Adults	1 (equivalent to 75 mg diclofenac sodium)	2 (equivalent to 150 mg diclofenac sodium)

Method of administration and duration of use:
Swiss Relief Dual Release is swallowed whole (without chewing) and with plenty of liquid.
Those with sensitive stomachs are recommended to take Swiss Relief Dual Release during meals.

The duration of use is decided by the treating physician.
For rheumatic diseases, it may be necessary to take Swiss Relief Dual Release over a prolonged period of time.

Undesirable effects can be minimised if the lowest effective dose required to achieve symptomatic control is used over the shortest possible period of time (see section 4.4 Special warnings and precautions for use).

Specific patient groups:

Elderly patients:
No specific dose adjustment is required. Due to the potential adverse effect profile, elderly patients should be monitored with particular care.

Impaired renal function:

Swiss relief dual release is contraindicated in patients with renal failure (see section 4.3 Contraindications).

No specific studies have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering Swiss Relief Dual release to patients with mild to moderate renal impairment (see section 4.4)

Hepatic impairment

Swiss relief dual release is contraindicated in patients with hepatic failure (see section 4.3 Contraindications).

No specific studies have been carried out in patients with hepatic impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering Swiss Relief Dual Release to patients with mild to moderate hepatic impairment (see section 4.4).

Established cardiovascular disease or significant cardiovascular risk factors

Swiss Relief Dual Release is contraindicated in patients with established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease (see section 4.3 Contraindications).

Patients with congestive heart failure (NYHA-1) and patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration and only at doses ≤100 mg daily when treatment continues for more than 4 weeks.

Paediatric population:
For use in children and adolescents, see also section 4.3.

4.3 Contraindications

- Hypersensitivity to the active substance diclofenac or to any of the excipients listed in section 6.1;
- Known reactions of bronchospasm, asthma, rhinitis or urticaria following previous ingestion of acetylsalicylic acid or other non-steroidal antirheumatic/anti-inflammatory drugs (NSAIDs);
- Unexplained haematopoietic disorders;
- Active or history of recurrent peptic ulcers or bleeding (at least 2 distinct episodes of proven ulceration or bleeding);
- History of gastrointestinal bleeding or perforation, associated with previous therapy with NSAIDs;
- Cerebrovascular or other active bleeding;
- Severe hepatic or renal dysfunction;
- Known congestive heart failure (NYHA II-IV), ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Severe heart failure;
- Pregnancy, in the last trimester (see section 4.6)

Swiss Relief Dual Release is not suitable for children and adolescents under 18 years of age, as the active substance level is too high.

4.4 Special warnings and precautions for use

Gastrointestinal safety:

The use of Swiss Relief Dual Release in combination with NSAIDs, including selective cyclooxygenase-2 inhibitors, should be avoided.

Undesirable effects can be reduced by using the lowest effective dose for the shortest period required to achieve symptomatic control (see section 4.2 and gastrointestinal and cardiovascular risks below).

NSAIDs, including diclofenac, may be associated with an increased risk of gastrointestinal anastomotic leakage. If diclofenac is used after surgery in the gastrointestinal tract, close medical surveillance and particular caution are recommended.

Elderly patients:

Undesirable effects are more common in elderly patients on NSAID therapy, especially gastrointestinal bleeding and perforation, sometimes with fatal outcome (see section 4.2).

Gastrointestinal bleeding, ulcers and perforations:

Gastrointestinal bleeding, ulcers or perforations, sometimes with fatal outcome, have been reported with all NSAIDs. They have occurred at any time during treatment, with or without previous warning symptoms or history of serious gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is greater with increasing NSAID doses, in patients with a history of ulcers, especially with complications of bleeding or perforation (see section 4.3), and in elderly patients. These patients should start the treatment at the lowest available dose.
For these patients, as well as for patients requiring concomitant therapy with low-dose acetylsalicylic acid (ASA) or other medicinal products that can increase the gastrointestinal risk (see section 4.5), combination therapy with protective medicines (e.g. misoprostol or proton pump inhibitors) should be considered (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, especially those of advanced age, should report any unusual abdominal symptoms (particularly gastrointestinal bleeding), especially at the start of treatment.
Caution is advised if patients are concomitantly receiving medicinal products that can increase the risk of ulcers or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or platelet

aggregation inhibitors such as ASA (see section 4.5).

Treatment must be discontinued if gastrointestinal bleeding or ulcers occur in patients receiving Swiss Relief Dual Release.

NSAIDs should only be used with caution in patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease), as their condition may deteriorate (see section 4.8).

Cardiovascular and cerebrovascular effects:

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

Clinical studies and epidemiological data suggest that the use of diclofenac, especially at a high dose (150 mg daily) and as part of long-term treatment, may be associated with a slightly increased risk of arterial thrombotic events (for example, myocardial infarction and stroke).

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 the dose and duration of use, the lowest effective daily dose should be used over the shortest possible period of time. It should be regularly checked whether the patient still requires symptomatic relief and how he/she is responding to treatment.

Skin reactions:

Very rarely during NSAID therapy, serious skin reactions, some with fatal outcome, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis (Lyell's syndrome), have been reported (see section 4.8). The risk of such reactions seems to be greatest at the start of therapy, as these reactions have occurred within in the first month of treatment in the majority of cases. At the first signs of skin rash, mucosal lesions or other signs of a hypersensitivity reaction, Swiss Relief Dual Release should be discontinued.

Hepatic effects:

Caution is advised prior to initiation of treatment in patients with hepatic dysfunction, as their condition may deteriorate during therapy with diclofenac. If Swiss Relief Dual Release is taken repeatedly or over prolonged periods, regular monitoring of liver function is indicated as a precaution. If clinical signs of liver disease are found, Swiss Relief Dual Release should be discontinued immediately.

Other information:

Swiss Relief Dual Release should be used only after strict assessment of the benefit/risk ratio:

- In congenital disorders of porphyrin metabolism (e.g. acute intermittent porphyria);
- In systemic lupus erythematosus (SLE) or in mixed connective tissue disease (see section 4.8).

Particularly careful medical surveillance is required in the following cases:

- impaired renal function;
- hepatic dysfunction;
- immediately following major surgery;
- patients with hay fever, nasal polyps or chronic obstructive pulmonary disease, as they are at greater risk of developing allergic reactions. These may manifest as asthma attacks (known as analgesic-induced asthma), angioedema or urticaria.
- patients who experience allergic reactions to other substances, as they are likewise at greater risk of developing hypersensitivity reactions when using Swiss Relief Dual release.

Severe acute hypersensitivity reactions (for example, anaphylactic shock) are observed very rarely. At the first signs of a hypersensitivity reaction after taking Swiss Relief Dual Release, treatment must be discontinued. Requisite medical procedures, depending on the symptoms, must be initiated by persons with the relevant professional expertise.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also rarely occur with diclofenac use without prior exposure to the medicine. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can lead to myocardial infarction. Symptoms of such reactions at the patient's presentation may include chest pain associated with an allergic reaction to diclofenac.

Diclofenac can temporarily inhibit platelet aggregation, Patients with coagulation disorders should therefore be carefully monitored.

As with other NSAIDs, diclofenac can mask the signs and symptoms of an infection due to its pharmacodynamic properties. If signs of infection appear for the first time or worsen while using Swiss Relief Dual Release, the patient is

therefore recommended to consult a physician immediately. It should be checked whether there is an indication for anti-infective/antibiotic treatment.

During prolonged administration of Swiss Relief Dual Release regular monitoring of kidney function and blood counts is required.

Headaches, which must not be treated with increased doses of the medicine, may occur with prolonged use of analgesics.

Generally speaking, the habitual use of analgesics, especially when several analgesic agents are combined, may lead to permanent kidney damage with the risk of renal failure (analgesic nephropathy).

During use of NSAIDs, undesirable effects due to the active substance, especially those affecting the gastrointestinal tract or the central nervous system, may be potentiated by concomitant consumption of alcohol.

Regarding female fertility, see section 4.6.

4.5 Interaction with other medicinal products and other forms of interaction

Other NSAIDs including salicylates:

Co-administration of several NSAIDs can increase the risk of gastrointestinal ulcers and bleeding, due to a synergistic effect. Concomitant use of diclofenac with other NSAIDs is therefore not recommended (see section 4.4).

Digoxin, phenytoin, lithium:
Concomitant use of Swiss Relief Dual Release and digoxin, phenytoin or lithium can increase the concentration of these medicines in the blood. Monitoring the serum lithium levels is necessary. Monitoring the serum digoxin and the serum phenytoin levels is recommended.

Diuretics, ACE inhibitors and angiotensin-II antagonists:

Non-steroidal anti-inflammatory drugs can attenuate the effect of diuretics and antihypertensive agents. In patients with impaired renal function (e.g. dehydrated patients or elderly patients with impaired renal function) concomitant ingestion of an ACE inhibitor or an angiotensin-II antagonist with a cyclooxygenase inhibitor can lead to further deterioration in renal function, including possibly acute renal failure, which is usually reversible. Hence, such a combination should only be used with caution, especially in elderly patients. Patients must be instructed to maintain adequate hydration and regular monitoring of kidney function tests should be considered following initiation of combination therapy.

Co-administration of Swiss Relief Dual Release and potassium-sparing diuretics can lead to hyperkalaemia. Hence, monitoring of the potassium level is recommended during concomitant therapy.

Glucocorticoids:

Increased risk of gastrointestinal ulcers or bleeding (see section 4.4).

Platelet aggregation inhibitors such as acetylsalicylic acid and selective serotonin reuptake inhibitors (SSRIs):

Increased risk of gastrointestinal bleeding (see section 4.4.).

Methotrexate:

Administration of Swiss Relief Dual Release within 24 hours before or after administration of methotrexate can lead to increased blood concentrations of methotrexate and an increase in its toxic effect.

Ciclosporin:

NSAIDs (like diclofenac sodium) can increase the nephrotoxicity of ciclosporin.

Anticoagulants and platelet aggregation inhibitors:

Caution is advised, as concomitant administration may increase the risk of bleeding. Although clinical studies do not appear to suggest that diclofenac influences the effect of anticoagulants, there are reports of an increased risk of bleeding in patients concomitantly receiving diclofenac and anticoagulants. Hence, close monitoring of these patients is recommended.

Probenecid and sulfinpyrazone:

Medicinal products containing probenecid or sulfinpyrazone can delay the excretion of diclofenac.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Inhibition of prostaglandin synthesis can have a negative effect on pregnancy and/or embryofetal development. Data from epidemiological studies indicate an increased risk of miscarriage, as well as cardiac malformation and gastroschisis, after the use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is assumed to increase with the dose and duration of therapy.

In animals it has been demonstrated, that administration of a prostaglandin synthesis inhibitor leads to increased pre- and post-implantation loss and embryofetal lethality. Furthermore, increased incidence of various malformations, including cardiovascular malformations, have been reported in animals receiving a prostaglandin synthesis inhibitor during the organogenesis phase.

During the first and second trimesters of pregnancy diclofenac should only be given when absolutely necessary. If diclofenac is used by a woman trying to conceive, or if used during the first or second trimester of pregnancy, the dose should be kept as low as possible, and the duration of treatment as short as possible.

During the third trimester of pregnancy all prostaglandin synthesis inhibitors can:

- expose the fetus to the following risks:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which can progress to renal failure with oligohydramnios;

- expose mother and child at the end of pregnancy to the following risks:

- possible prolongation of the bleeding time, an effect resulting from platelet aggregation inhibition, which can occur even at very low d0oses;
- inhibition of uterine contractions, resulting in delayed or prolonged labour.

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

Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs, including Swiss Relief Dual Release, in pregnant women at about 28 weeks gestation and later. NSAIDs, including Swiss Relief Dual Release, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs, including Swiss Relief Dual Release, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 28 weeks gestation, limit Swiss Relief Dual Release use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if Swiss Relief Dual Release treatment extends beyond 5 days. Discontinue Swiss Relief Dual Release if oligohydramnios occurs and follow up according to clinical practice.

Breast-feeding:

The active substance diclofenac and its metabolites are excreted in human milk in small amounts. As no harmful consequences for the infant have been reported to date, interruption of breast-feeding is generally not required in short-term use. However, if prolonged use/intake of higher doses is prescribed for the treatment of rheumatic disorders, early weaning should be considered.

Fertility:
The use of Swiss Relief Dual Release, as with the use of other medicinal products known to inhibit cyclooxygenase/prostaglandin synthesis, can impair female fertility and is therefore not recommended for women wishing to conceive. Discontinuation of Swiss Relief Dual Release should be considered for women having difficulties conceiving or who are undergoing infertility tests.

4.7 Effects on ability to drive and use machines
As adverse CNS effects such as fatigue and dizziness, can occur during use of Swiss Relief Dual Release, particularly at higher doses, reaction skills may be altered in individual cases and ability to drive and use machines may be impaired. This applies particularly applies in interaction with alcohol.

4.8 Undesirable effects

The following categories are used for the evaluation of adverse reactions:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

It must be remembered that the following adverse drug reactions are predominantly dose-dependent and interindividually different.

The most commonly observed adverse reactions concern the digestive tract. Peptic ulcers, perforation or bleeding, sometimes fatal, may occur, especially in elderly patients (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, worsening of colitis and Crohn's disease (see section 4.4) have been reported following use. Gastritis has been observed less frequently.

Oedema, hypertension and heart failure have been reported in association with NSAID treatment.

Clinical studies and epidemiological data are consistent in their suggestion of an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, especially at a high dose (150mg daily) and in long term use (see section 4.3 and 4.4 regarding Contraindications and Special warnings and special precautions for use).

Cardiac disorders:
Very rare: palpitations, oedema, heart failure, myocardial infarction.
Not known: Kounis syndrome.

Blood and lymphatic system disorders:
Very rare: haematopoietic disorders (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis), haemolytic anaemia.
Initial signs may be: fever, sore throat, superficial oral lesions, influenza-like symptoms, severe exhaustion, epistaxis and bleeding into the skin.

In long-term treatment, blood count should be regularly monitored.

Nervous system disorders:
Common: central nervous system disorders such as headaches, dizziness, light-headedness, agitation, irritability or fatigue.
Very rare: paraesthesia, dysgeusia, memory impairment, disorientation, seizures, tremor.

Eye disorders:
Very rare: visual disturbances (blurred vision and diplopia).

Ear and labyrinth disorders:
Very rare: tinnitus, transient hearing impairment.

Gastrointestinal disorders:
Very common: gastrointestinal complaints such as nausea, vomiting and diarrhoea, as well as minor gastrointestinal blood loss, which can cause anaemia in exceptional cases.
Common: dyspepsia, flatulence, abdominal cramps, loss of appetite and gastrointestinal ulcers (sometimes with bleeding and perforation).
Uncommon: haematemesis, melaena or bloody diarrhoea,
Very rare: stomatitis, glossitis, oesophageal lesions, lower abdominal complaints (e.g. haemorrhagic colitis or exacerbation of ulcerative colitis or Crohn's disease), constipation, pancreatitis, diaphragm-like intestinal strictures.
Not known: ischaemic colitis.

The patient must be instructed to discontinue the medicine and consult a physician immediately at the onset of moderately severe epigastric pain or in the event of melaena or haematemesis.

Renal and urinary disorders:
Uncommon: oedema formation, especially in patients with hypertension or renal impairment.
Very rare: renal tissue damage (interstitial nephritis, papillary necrosis), which may be accompanied by acute renal impairment, proteinuria and/or haematuria. Nephrotic syndrome.
Renal function should therefore be regularly monitored.

Skin and subcutaneous tissue disorders:
Uncommon: alopecia.
Very rare: exanthema, eczema, erythema, photosensitisation, purpura (including allergic purpura) and bullous skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome).

Infections and infestations:
Very rarely, worsening of infection-related inflammation (e.g. development of necrotising fasciitis) has been described in temporal association with the systemic use of NSAIDs. This is possibly related to the mechanism of action of NSAIDs.

If signs of infection appear for the first time or worsen while using Swiss Relief Dual Release, the patient is therefore recommended to consult a physician immediately. It should be checked whether there is an indication for anti-infective/antibiotic treatment.

Very rarely, symptoms of aseptic meningitis with nuchal rigidity, headache, nausea, vomiting, fever or clouded consciousness have been observed during the use of diclofenac. Patients with autoimmune disorders (SLE, mixed connective tissue disease) seem to be predisposed.

Vascular disorders:
Very rare: hypertension.

Immune system disorders:
Common: hypersensitivity reactions such as skin rash and pruritus.
Uncommon: urticaria.

In this case, the patient must be instructed to inform the physician immediately and to stop taking Swiss Relief Dual Release.

Very rare: severe generalised hypersensitivity reactions. They may manifest as facial oedema, swollen tongue, inner laryngeal swelling with airway constriction, dyspnoea, tachycardia, drop in blood pressure and even life-threating shock.

If any of these symptoms occur, which may happen even during initial use, the patient must stop taking Swiss Relief Dual Release and immediate medical assistance is required.

Very rare: allergic vasculitis and pneumonitis.

Hepatobiliary disorders:
Common: elevated serum transaminases.
Uncommon: liver damage, especially in long-term therapy, acute hepatitis with or without jaundice (fulminant in very rarely cases, even without prodromal symptoms).
Liver function tests should therefore be regularly monitored in long-term therapy.

Psychiatric disorders:
Very rare: psychotic reactions, depression, feelings of anxiety, nightmares.

Swiss Relief Dual Release can very rarely cause allergic reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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
In addition, you can report to Padagis.co.il

4.9 Overdose

a) Symptoms of an overdose:

Central nervous system disorders may occur as symptoms of an overdose, such as headache, dizziness, light-headedness, and loss of consciousness (in children, also myoclonic seizures), as well as abdominal pain, nausea and vomiting. Furthermore, gastrointestinal bleeding, hepatic dysfunction and renal dysfunction are possible. Hypotension, respiratory depression and cyanosis may also occur.

b) Therapeutic measures in the event of overdose:

There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Non-steroidal anti-inflammatory, and antirheumatic drugs;
Acetic acid derivatives and related substances
ATC code: M01AB05

Diclofenac is a non-steroidal anti-inflammatory/antirheumatic agent, which has been shown to be effective in the usual experimental animal models of inflammation through inhibition of prostaglandin synthesis. In humans, diclofenac reduces inflammation-induced pain, swelling and fever. Furthermore, diclofenac inhibits ADP- and collagen- induced platelet aggregation.

5.2 Pharmacokinetic properties

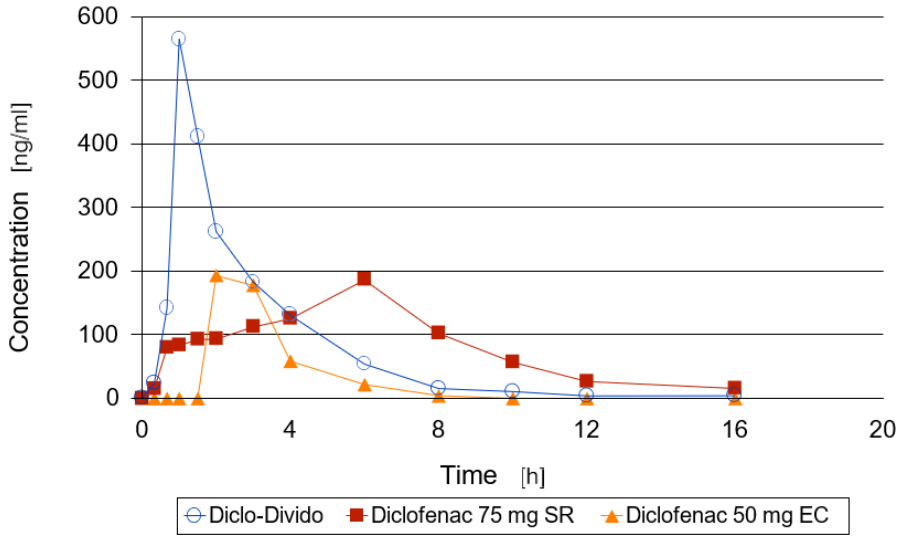
Following oral administration of the usual gastro-resistant formulations, diclofenac is completely absorbed distally from the stomach. Depending on the gastric transit time, peak plasma levels are reached after 1-16 hours; on average, after 2-3 hours. Following IM administration, peak plasma levels are reached after 10-20 minutes; following rectal administration, after approximately 30 minutes. Orally administered diclofenac is subject to a significant first-pass effect; only 35 - 70% of the absorbed active substance reaches the post-hepatic circulation in unchanged form. Around 30% of the active substance is excreted in metabolised form with the faeces.
Following hepatic conversion (hydroxylation and conjugation), around 70% is renally eliminated as pharmacologically inactive metabolites. The elimination half-life, which is largely independent of liver and renal function, is about 2 hours. Plasma protein binding is about 99%.

Bioavailability
A bioavailability study performed in 1992 with Diclofenac-Divido 75 mg in 24 subjects showed in comparison to reference products (Diclofenac 50 mg EC [gastro-resistant tablets] and Diclofenac 75 mg SR [prolonged-release tablets]):

	Investigational product Diclofenac-Divido 75 mg* prolonged-release capsule	Reference product Diclofenac 50 mg EC	Reference product Diclofenac 75 mg SR
Peak plasma concentration (c_{max}) [ng/ml] range:	869.3 232.1 – 1652.3	1003.0 0.0 - 2152.1	289.9 144.3 - 1160.9
Time to peak plasma concentration (t_{max}) [h] range:	1.00 0.67 - 2.00	2.00 1.5 - 6.00	6.0 0.33 - 8.00
Area under the concentration-time curve ($AUC_{0-\infty}$) [h · ng/ml] range:	1473.1 787.5 - 3592.1	1315.7 0.00 - 2798.3	1428.4 741.4 - 2973.2

* Composition identical to Swiss Relief Dual Release

Mean progression of plasma levels for Diclofenac-Divido 75 mg (Diclo-Divido)* compared with a reference product in a concentration-time diagram:



*Composition identical to Swiss Relief Dual Release

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential, other than that already described in other sections of the Summary of Product Characteristics. The chronic toxicity of diclofenac in animal trials mainly manifested in the form of lesions and ulcers in the gastrointestinal tract. In a 2-year toxicity study, a dose-dependent increase in thrombotic vascular occlusions was observed in the heart of rats treated with diclofenac.

In animal reproduction toxicity studies, diclofenac led to inhibited ovulation in the rabbit, as well as disturbances in implantation and early embryonic development in the rat. Gestation and duration of parturition were prolonged by diclofenac. The embryotoxic potential of diclofenac was studied in three animal species (rat, mouse and rabbit). Death of the embryo and growth retardation occurred at doses within the maternally toxic range. Based on the data available, diclofenac is regarded as non-teratogenic. Doses below the maternally toxic limit had no influence on the postnatal development of the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

microcrystalline cellulose,
gelatin,
povidone K 25,
methacrylic acid ethyl acrylate copolymer (1:1) neutralized with sodium hydroxide,
talc,
ammonio methacrylate copolymer (type B),
colloidal anhydrous silica,
propylene glycol,
ammonio methacrylate copolymer (type A),

titanium dioxide E 171,
triethylcitrate,
indigocarmine E 132,
sodium lauryl sulphate,
printing ink

6.2 Incompatibilities

None known to date.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
This medicinal product must not be used after the expiry date.

6.4 Special precautions for storage

Store below 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Blisters made of PVC/PVDC foil and aluminium foil.
Original pack with 4, 10, 20, 56, hard capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MANUFACTURER

Swiss Caps GMBH
Grassingstrasse 9, 83043 Bad Aibling, Germany

8. LICENSE HOLDER

Padagis Israel Agencies Ltd., 1 Rakefet St., Shoham, Israel

9. LICENSE NUMBER

142-10-31815

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19/12/2021