# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Diclo-SSP 50 (Diclofenac sodium enteric coated Tablets BP 50 mg)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric coated tablet contains 50 mg Diclofenac sodium.

Excipients with known effect: lactose

For the full list of excipients see section 6.1.

## 3. PHARMACEUTICAL FORM

Brown, round biconvex tablet.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

Diclofenac sodium enteric-coated tablets are used for relief of all grades of pain and inflammation in a wide range of conditions, including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, acute musculo-skeletal disorders such as periarthritis (for example frozen shoulder), tendinitis, tenosynovitis, bursitis, other painful conditions resulting from trauma, including fracture, low back pain, sprains, strains, dislocations, orthopaedic, dental and other minor surgery.

### 4.2. Posology and method of administration

Posology

**Usual Adult Dose for Rheumatoid Arthritis:**

Diclofenac sodium enteric-coated tablets: 50 mg orally 3 to 4 times a day Maximum dose: 225 mg daily this would be for the rare patient in whom the benefits outweigh the clinical risks. For the relief of signs and symptoms of rheumatoid arthritis

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**Method of administration**

Oral; the tablets should be swallowed with a drink of water.

### 4.3. Contraindications

Hypersensitivity to cimetidine 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

Severe hepatic, renal or cardiac failure.

Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.

Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

**4.4. Special warnings and precautions for use**

NSAIDs may cause an increased risk of serious CV thrombotic events, MI, an stroke,which can be fatal. This risk may increase with length of therapy. Patients with CVdisease or risk factors for CV disease may be at greater risk. NSAIDs cause an increased risk of serious GI adverse reactions, including bleeding, inflammation,perforation of the stomach or intestines, and ulceration, which can be fatal. These events can occur any time during use and without warning

symptoms. Elderly patients are at greater risk of serious GI events. Diclofenac sodium should be used with caution in patients with intrinsic coagulation defects and those on anticoagulant therapy. It should be used with caution in patientswith compromised cardiac function, hypertension and other conditions predisposing to fluid retention. It should be used with extra care in the presence of existinguncontrolled infection. Discontinue drug if skin reaction occurs.

**4.5. Interaction with other medicinal products and other forms of interaction**

**Anti-hypertensives:**

Reduced anti-hypertensive effect. Cardiac Glycosides and Lithium:

The plasma concentration of digoxin and lithium may be increased. NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

**Anticoagulants:**

Although clinical investigations do not appear to indicate that Diclofenac has an influence on the effect of anticoagulants, there are isolated reports of an increased risk of haemorrhage with the combined use of Diclofenac and anticoagulant therapy. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is necessary. As with other non-steroidal antiinflammatory agents, Diclofenac can reversibly inhibit platelet aggregation.

**Hypoglycaemics:**

Diclofenac does not appear to potentiate the effect of oral hypoglycaemics. However, caution is advised in patients receiving such combinations of treatment and close monitoring of such patients is required.

**Cyclosporin:**

Cyclosporin nephrotoxicity may be increased by the effect of nonsteroidal anti-inflammatory drugs on renal prostaglandins.

Mifepristone:

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

**Methotrexate**:

Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other, since NSAIDs may increase methotrexate plasma levels, resulting in increased toxicity.

**Quinolone anti-microbials:**

Concomitant therapy with quinolone antimicrobials, may cause convulsions. This may occur in patients with or without a previous history of epilepsy or convulsions. Thus caution is needed if introducing a quinolone antimicrobial to a patient already taking an NSAID.

## 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. If diclofenac is used by a woman attempting to conceive, or during the 1st trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

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

**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.

## 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 drug reactions are classified as follows:

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)

The following undesirable effects include those reported with diclofenac enteric coated tablets and/or other dosage forms of diclofenac during short-term and long-term use.

Please note that the following adverse drug reactions are mostly dose-dependent and may differ from individual to individual.

The most common adverse drug reactions affect the digestive tract. Peptic ulcers, perforation or bleeding, sometimes fatal, may occur, particularly in elderly patients (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, indigestion, abdominal pain, melena, hematemesis, ulcerative stomatitis, exacerbation of ulcerative colitis and Crohn's disease (see section 4.4) have been reported after use.

Gastritis is less common.

Oedema, high blood pressure and heart failure have been reported in response to NSAID treatment, including diclofenac.

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 .

*Cardiac disorders*

Uncommon*: cardiac infarction, heart failure, palpitations, chest pain

Very rare: oedema

Not known: Kounis syndrome

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

Blood and lymphatic system disorders

Very rare: impaired haematopoiesis (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis) haemolytic anaemia, aplastic anaemia

Initial symptoms could be: fever, sore throat, superficial lesions in the mouth, influenza-like complaints, severe lassitude, nose bleeding and dermatorrhagia.

The blood count should be monitored regularly during long-term therapy.

*Nervous system disorders*

Common: central nervous symptoms such as headache, vertigo, light-headedness, state of excitement, irritability or fatigue

Very rare: sensory disturbances, distortion of taste, impaired memory, disorientation, seizures, tremor, stroke

*Eye disorders*

Very rare: impaired vision (blurred and double vision)

Ear and labyrinth disorders

Common: vertigo

Very rare: tinnitus, temporary impaired hearing

*Gastrointestinal disorders*

Very common: gastrointestinal complaints such as nausea, vomiting and diarrhoea as well as minor gastrointestinal bleeding, which may cause anaemia in individual cases

Common: dyspepsia, flatulence, abdominal pain, abdominal cramps, loss of appetite as well as gastric or intestinal ulcers (sometimes with bleeding and perforation)

Uncommon: hematemesis, melena or bloody diarrhoea

Rare: gastritis

Very rare: stomatitis (including ulcerative stomatitis), glossitis, lesions of the oesophagus, lower abdominal complaints (e.g. colitis, haemorrhaging inflammation of the colon or exacerbation of ulcerative colitis or Crohn's disease), constipation, pancreatitis, diaphragm-like intestinal strictures

Unknown: ischaemic colitis

The patient should be instructed to stop taking the medication if he experiences severe upper abdominal pain, melena or hematemesis and to seek medical help immediately.

*Renal and urinary disorders*

Uncommon: development of oedema especially in patients with arterial hypertension or renal failure

Very rare: renal tissue damage (interstitial nephritis, papillary necrosis) that may be associated with acute renal failure, proteinuria and/or haematuria, nephrotic syndrome, acute renal failure

Renal function should therefore be monitored regularly.

*Skin and subcutaneous tissue disorders*

Common: rash

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 syndrome), dermatitis exfoliative, erythrodermia

Infections and infestations

There have been very rare reports of exacerbation of infective inflammations (e.g. development of necrotic fasciitis) in association with systemic use of NSAIDs. This could be related to the

mechanism of action of NSAIDs.

If signs of an infection occur or worsen during treatment with diclofenac, the patient is advised to consult a doctor without delay. It should be checked whether anti-infective or antibiotic therapy is indicated.

In very rare cases, the use of diclofenac has been associated with symptoms of aseptic meningitis such as stiff neck, headache, nausea, vomiting, fever or clouding of consciousness. Patients with autoimmune diseases, such as SLE or mixed connective tissue disease, seem to be predisposed to this.

*Vascular disorders*

Very rare: hypertension, vasculitis

Immune system disorders

Common: hypersensitivity reactions such as skin rash and itching

Uncommon: urticaria

In such a case, the patient is advised to contact a doctor immediately and to stop taking diclofenac.

Rare: anaphylactic and anaphylactoid reactions (including hypotension and shock)

Very rare: Severe general hypersensitivity reactions such as angioedema (including facial oedema), swelling of the tongue, inner swelling of the larynx with restriction of the respiratory passages, laboured breathing, palpitations, fall in blood pressure and eventually life-threatening shock.

If any of these symptoms occur, and this is possible following the first administration, immediate medical attention is required, and diclofenac should be discontinued.

Very rare: allergic vasculitis and pneumonitis

*Hepatobiliary disorders*

Common: rise in serum transaminases

Uncommon: liver damage, especially during long-term therapy, acute hepatitis with or without icterus (in very rare cases taking a fulminant course, sometimes without prodromal symptoms)

Very rare: hepatic necrosis, hepatic failure

Regular monitoring of liver parameters is therefore necessary during long-term therapy.

*Psychiatric disorders*

Very rare: psychotic reactions, depression, feelings of anxiety, nightmares, insomnia

*Respiratory, thoracic and mediastinal disorders*

Rare: asthma (including dyspnoea)

Very rare: pneumonitis

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

**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.

*Treatment*

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: Non-steroidal antiphlogistic and antirheumatic agent; acetic acid derivative and related substances. ATC Code: M01AB05.

**Mechanism of action**

Diclofenac is a non-steroidal antiphlogistic/antirheumatic agent which proved to be effective in standard animal experiments on inflammation by inhibiting prostaglandin synthesis. In humans diclofenac reduces inflammatory pain, swelling and fever. Diclofenac also inhibits ADP and collagen-induced platelet aggregation.

**Paediatric population**

Limited experience is available from clinical studies on the use of diclofenac for juvenile rheumatoid arthritis (JRA)/juvenile idiopathic arthritis (JIA) in children and adolescents. In a randomised, doubleblind, 2-week parallel-group study in children aged 3 to 15 years with JRA/JIA, the efficacy and safety of diclofenac was compared at a dosage of 2 to 3 mg/kg body weight daily with acetylsalicylic acid (ASA, 50 to 100 mg/kg body weight daily) and placebo (15 patients in each group). The evaluation showed that 11 out of 15 diclofenac-treated patients, 6 out of 12 ASA-treated patients and 4 out of 15 placebo-treated patients showed improvements with statistically significant ($p<0.05$) differences. The number of sensitive joints decreased with diclofenac and ASA, but increased with placebo. In a second randomised, double-blind, 6-week parallel-group study in children aged 4 to 15 years with JRA/JIA, the efficacy and safety of diclofenac (daily dosage of 2 to 3 mg/kg body weight, n=22) was comparable with that of indomethacin (daily dosage of 2 to 3 mg/kg body weight, n=23).

### 5.2. Pharmacokinetic properties

**Absorption and distribution**

After oral application of the standard enteric coated pharmaceutical form, diclofenac is completely absorbed distally from the stomach. Maximum plasma levels are reached within 1-16 hours depending on how long passage through the stomach takes and are reached on average within 2–3

hours. Maximum plasma levels are reached within 10 – 20 minutes after IM administration and approx. 30 minutes after rectal administration. The plasma protein binding is approx. 99 %.

**Metabolism and elimination**

Orally administered diclofenac is clearly subject to a first pass effect; only 35–70 % of the absorbed active ingredient reaches post-hepatic circulation in unchanged form. Approx. 30 % of the active ingredient is metabolised and excreted in the faeces.

Approximately 70% is eliminated renally after hepatic metabolisation (hydroxylisation and conjugation) in the form of pharmacologically inactive metabolites. Largely independent of hepatic and renal function, the elimination half-life is approximately 2 hours.

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.

**5.3. Preclinical safety data**

Based on conventional studies on safety pharmacology, genotoxicity and carcinogenic potential, preclinical data have revealed no special hazard for humans beyond those addressed in other sections. In animal studies chronic toxicity of diclofenac was characterised predominately as gastrointestinal lesions and ulcers. In a two-year toxicity study a dose-dependent increase in thrombotic vascular occlusion of the heart was observed in rats treated with diclofenac.

In studies on reproductive toxicity in animals diclofenac was observed to inhibit ovulation in the rabbit and interfere with implantation and early embryonal development in the rat. The duration of pregnancy and labour were prolonged by diclofenac. The embryotoxic potential of diclofenac was investigated in three animal species (rat, mouse, rabbit). Foetal death and growth retardation occurred at doses in the maternal-toxic range. Based on the available data, diclofenac is considered non-teratogenic. Doses below the maternal-toxic limit had no effect on the postnatal development of the offspring.

## 6. PHARMACEUTICAL PARTICULARS

**6.1. List of excipients**

**Core Tablet**

Croscarmellose Sodium- BP

Lactose NF fast flow BMS 35957

Microcrystalline cellulose PH 102-BP

Silicon Dioxide- BP

Magnesium Stearate- BP

**Coating**

Brown enteric coating premix

**6.2. Incompatibilities**

Not applicable.

**6.3. Shelf life**

3 years

**6.4. Special precautions for storage**

Store below 30°C, protect from light and moisture.

**6.5. Nature and contents of container**

Clear and colourless PVC /Aluminium blisters containing tablets. 10 tablets per blister and 5 blisters in box (10x5) or 10 tablets per blister and 10 blisters in box (10x10).

**6.6. Special precautions for disposal**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

SANSHENG PHARMACEUTICAL PLC

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**8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS**

*07153/07920/NMR/2019*

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

*01/03/2022*

**10. DATE OF REVISION OF THE TEXT**

01/08/2023