SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PRODUCT

Clofenac SR Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACTIVE INGREDIENTS	PER TABLET (MG)
Diclofenac Sodium	100 mg

Kindly refer to Section 6.1 for excipient.

3. PHARMACEUTICAL FORM

Round, pink film-coated, bevel-edged with shallow convex faces.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Used for relief of pain and inflammation in conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout and following some surgical procedures.

4.2 Posology and Method of administration

As a general recommendation, the dose should be individually adjusted. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section WARNING AND PRECAUTIONS).

Established cardiovascular disease or significant cardiovascular risk factors

Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking) should be treated with diclofenac only after careful consideration and only at doses ≤100 mg daily if treated for more than 4 weeks (see section WARNING AND PRECAUTIONS)

Adults:

Oral, one 100 mg tablet a day. Tablets should be swallowed whole preferably with food.

Elderly:

Care should be used when treating patients who are frail or have a low body weight as they will in general be more susceptible to adverse reactions. The lowest effective dose should be used in these patients. The standard adult dose may be used for other elderly patients.

Children:

Not suitable for use in children.

Contraindication

- Contraindicated in patients known to be hypersensitive to Diclofenac sodium.
- Contraindicated in patients who when taking aspirin or other non-steroidal anti-inflammatory drugs suffer attacks of asthma, urticaria or acute rhinitis.
- Should not be used in patients with active or suspected peptic ulcer or gastrointestinal bleeding
- Contraindicated in patients with bone marrow depression.
- Severe cardiac failure (see section WARNING and PRECAUTIONS).

Warnings and precautions

- Patients with a history of gastrointestinal ulceration, haematemesis or melaena should be carefully observed.
- Care should be taken when treating patients with ulcerative colitis, Crohn's disease, haematological abnormalities or bleeding diathesis.
- Caution is recommended in elderly patients and those with renal or hepatic impairment. Monitoring of renal function, hepatic function and blood counts should be performed on long-term NSAID patients, as a precautionary measure.
- Diclofenac sodium may trigger an attack in patients with hepatic porphyria.
- Patients should not drive or operate machinery if the experience dizziness or other central nervous system disturbances.
- Caution in patients who must restrict their sodium intake.
- Diclofenac should be stopped if liver function tests show abnormalities which persist or worsen, or if liver disease develops or if other symptoms such as eosinophilia or rash occur.
- Severe cutaneous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome) have been reported with diclofenac sodium. Patients treated with diclofenac sodium should be closely monitored for sign of hypersentivity reactions. Discontinue diclofenac sodium immediately if rash occurs.

Cardiovascular effects

Treatment with NSAIDs including diclofenac, particularly at high dose and in long term, may be associated with an increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke).

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As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest duration possible. The patient's need for symptomatic relief and response to therapy should be re-evaluated periosically, especially when treatment continues for more than 4 weeks.

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.

RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAID

Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAIDs therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious adverse events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

Drug Interactions

- Diclofenac may increase plasma concentrations of lithium, digoxin and methotrexate.
- Concomitant use of diclofenac sodium and other NSAIDs may increase the frequency of side effects.
- Diclofenac may increase cyclosporin nephrotoxicity as a result of their effect on renal prostaglandins.
- There is an increased risk of convulsions if quinolone antibiotics are given while Diclofenac is being taken, and caution is advised when considering their use.
- Increased serum potassium levels may result when Diclofenac is given concomitantly with potassium-sparing diuretics. Serum potassium levels should therefore be monitored.
- Care is required when giving anticoagulants with Diclofenac as it may reversibly inhibit platelet aggregation.
- Non-steroidal anti-inflammatory drugs (NSAIDs) may increase the hypoglycemic effect of antidiabetic agents; dosage adjustments of the diabetic agent may be necessary; glipizide and glyburide may not be affected as much as the other oral antidiabetic agents, however, caution with concurrent use is recommended. Diclofenac has also been reported to decrease the effects of antidiabetic agents, leading to hyperglycemia.

4.6 Pregnancy and lactation

The use of diclofenac sodium is not advisable in pregnancy and lactation.

4.7 Effects on ability to drive and use machines

Not applicable.

Main Side/ Adverse Effects

- Common side effects include nausea, headaches, diarrhoea, epigastric pain, anorexia, dyspepsia, flatulence, abdominal cramps, vertigo and dizziness.
- Skin rashes and eruptions have occasionally been reported and rarely urticaria.
- Isolated effects on the central nervous system include drowsiness, tiredness, impaired hearing, insomnia, irritability, anxiety etc.
- Occasional effects on the kidney include acute renal insufficiency, urinary abnormalities (eg. haematuria, proteinuria), nephrotic syndrome, papillary necrosis and interstitial nephritis.
- Effects on the liver include occasional reports of elevation of serum aminotransferase enzymes (ALT, AST) and rarely liver function disorders.
- Leucopenia, haemolytic anaemia, thrombocytopenia, aplastic anaemia and agranulocytosis have rarely been reported.
- Hypersensitivity reactions (anaphylactic/anaphylactoid systemic reactions, hypotension, and bronchospasm) have rarely been reported.
- Many of these cardiovascular effects may occur secondary to NSAID-induced renal function impairment: angina pectoris, irregular heartbeat, congestive heart failure, increased blood pressure and nose bleeds.
- Cases of hair loss, bullous eruptions, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) and photosensitivity reactions have been reported.

Cardiac disorders

- Uncommon*: Myocardial infarction, cardiac failure, palpitations, chest pain.
  *The frequency reflects data from long-term treatment with a high dose (150mg/day)

Description of selected adverse drug reactions

Arteriothrombotic events

Meta-analysis and pharmacoepidemiological data point towards an increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150mg daily) and during long-term treatment (see section WARNING AND PRECAUTIONS).

4.9 Overdose

Clinical features: Gastrointestinal symptoms (e.g. abdominal pain, nausea, vomiting); central nervous system effects (eg. lethargy, drowsiness) and renal effects have been reported. More serious effects such as gastrointestinal hemorrhage, acute renal failure, convulsions and coma have also been reported.

Treatment for overdosage: Gastric lavage and treatment with activated charcoal should be used as soon as possible after overdosage in order to prevent absorption of the drug. Further treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Diclofenac Sodium is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. It inhibits the activity of the enzyme cyclo-oxygenase, resulting in decreased formation of precursors of prostaglandins and thromboxanes from arachidonic acid.

As an analgesic, Diclofenac Sodium may block pain impulse generation via a peripheral action that may involve reduction of the activity of prostaglandins, and possibly inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation.

Diclofenac Sodium probably produce antipyresis by acting centrally on the hypothalamic heat-regulating center to produce peripheral vasodilation, resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves reduction of prostaglandin activity in the hypothalamus.

Pharmacokinetic properties

Clofenac SR tablets are slow release preparations designed to release Diclofenac over a period of time.

Absorption

Diclofenac is rapidly absorbed after oral administration. Although orally-administered Diclofenac is almost completely absorbed, it is subject to first-pass metabolism so that only 50 to 60% of the drug reaches the systemic circulation in the unchanged form.

Distribution

Diclofenac penetrates synovial fluid. It was detected in the synovial fluid 2 hours after a dose and the concentration remained relatively constant for the next 9 hours. It also readily crosses the placenta.

Diclofenac is excreted in breast milk. In one study, long-term use of 150 mg per day produced concentrations of 100 nanograms per mL in the breast milk. An infant of 4 to 5 kg consuming one liter per day would therefore ingest approximately 0.03 mg/kg per day.

Protein Binding
Diclofenac is highly protein bound. At therapeutic concentrations it is more than 99% bound to plasma proteins.

Half-life
The terminal plasma half-life is about 1 to 2 hours.

Metabolism
Diclofenac undergoes first-pass metabolism. It is metabolised to 4'-hydroxydiclofenac, 5-hydroxydiclofenac, 3'-hydroxydiclofenac and 4',5-dihydroxydiclofenac.

Excretion
It is excreted in the form of glucuronide and sulphate conjugates, mainly in the urine but also in the bile. About 40-65% of dose undergoes renal elimination and about 35% of dose undergoes biliary/faecal elimination. Little or none is eliminated unchanged via the renal or biliary systems.

Preclinical Safety Data
NOT APPLICABLE

6. PHARMACEUTICAL PARTICULARS

List of excipients
Xanthan Gum
Microcrystalline Cellulose
Magnesium Stearate
Isopropyl Alcohol
Propylene Glycol
Ponceau 4R Lake
Iron Oxide Red
Talc
Titanium Dioxide
Hydroxypropyl Methylcellulose E-5
Hydroxypropyl Methylcellulose E-15

Incompatibilities
NOT APPLICABLE

Shelf life
3 years from date of manufacture

Special precaution for storage
Store below 30˚C. Protect from moisture.

Nature and contents of container

Primary Packaging

Blister Pack

Type

Push-through blister pack; the package consists of a transparent thermoformable plastic material and a heat-sealable lacquered backing material.

Rigid Polyvinyl chloride (PVC) Film

Description	:	Polyvinylchloride (PVC) Film
Appearance	:	Glass clear transparent film

Aluminium blister foil

Description	:	Aluminium foil with high slip primer on bright surface and heat seal on matt surface/Aluminium foil with high slip primer on matt surface and heat seal on bright surface
Appearance	:	Bright surface/Matt surface each side
Heat Seal Lacquer	:	Heat Seal Lacquer surface is present on plain surface

Secondary Packaging Components
Outer Container/Packaging
Type: Unit box
Material: Paper carton

Instructions for use and handling <and disposal>

NOT APPLICABLE

7. MARKETING AUTHORISATION HOLDER

Name: HOVID Bhd.
Address : 121, Jalan Tunku Abdul Rahman,
(Jalan Kuala Kangsar)
30010 Ipoh, Perak, Malaysia

Manufacturer Name :

Name	:	HOVID Bhd.
Address	:	Lot 56442, 7 ½ Miles, Jalan Ipoh / Chemor, 31200 Chemor, Perak., Malaysia.

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

05726/06914/REN/2018

9. DATE OF FIRST AUTHORISATION

2018

10. DATE OF REVISION OF THE TEXT

June 2020