SUMMARY OF PRODUCT CHARACTERSTICS

DICLOFENAC SODIUM INJECTION 75MG/2ML

Summary of Product Characteristics| Cisen Pharmaceuticals co., ltd

1. Name of the medicinal product

Generic Name: Diclofenac Sodium Injection 75 mg/2 ml

2. Qualitative and quantitative composition

Diclofenac Sodium Injection 75 mg/2 ml contain diclofenac sodium 75 mg

Lidocaine hydrochloride BP 20mg
1, 2 Propylene Glycol 0.3 ml
Polyethylene Glycol 400 0.42 ml
Sodium Sulfite 6mg
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Small volume parenteral.
Colorless or almost colorless solution, USP Type I brown glass ampoules

4. Clinical particulars

4.1 Therapeutic indications

Diclofenac Sodium Injection is indicated for the treatment of painful condition, such as kidney stone pain, osteoarthritis (degeneration of joints) and rheumatoid arthritis (inflammation of joints), back pain, gout) formation of crystals in joints), injuries and fractures in children aged over 12 years, adults and older patients.

4.2 Posology and method of administration

Posology and Method of administration

Use for the shortest duration consistent with individual patient treatment goals.

For intravenous administration only.

For the treatment of acute pain, the recommended dose of Diclofenac Sodium Injectionis 37.5 mg administered by intravenous bolus injection over 15 seconds every 6 hours as needed, not to exceed 150 mg/day.

To reduce the risk of renal adverse reactions, patients must be well hydrated prior to administration of Diclofenac Sodium Injection.

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration. If visibly opaque particles, discoloration or other foreign particles are observed, the solution should not be used.

4.3 Contraindications

Diclofenac Sodium Injection is contraindicated in patients with:

 known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to diclofenac.

 A history of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal anaphylactic-like reactions to NSAIDs have been reported in such patients.

 perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

 moderate to severe renal insufficiency in the perioperative period and who are at risk for volume depletion.

4.4 Special warnings and precautions for use

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious gastrointestinal (GI) events.

Gastrointestinal Effects: Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including Diclofenac Sodium Injection, can cause serious GI adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at sometime during the course of therapy. Dyloject is administered by intravenous injection and is intended for acute short term use. However, even short-term therapy is not without risk.

Prescribe NSAIDs, including Diclofenac Sodium Injection, with extreme caution in those with a prior history of ulcer disease or GI bleeding. Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to treated patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most reports of spontaneous fatal GI events are in elderly or debilitated patients, and therefore special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, use the lowest effective dose for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Use caution when initiating treatment with Diclofenac Sodium Injectionin patients with considerable dehydration. Diclofenac Sodium Injectionis not recommended in patients with moderate to severe renal insufficiency and is contraindicated in patients with moderateto severe renal insufficiency in the perioperative period and who are at risk for volume depletion. Acute renal decompensation was observed in 4% out of 68 patients enrolled with renal impairment and treated with Diclofenac Sodium Injectionin clinical trials in the perioperative period.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance ofrenal perfusion. In these patients, administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Hepatic Effects

Elevations of one or more liver tests may occur during therapy with Diclofenac Sodium Injection. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (i.e., less than 3 times the ULN [ULN = the upper limit of the normal range]) or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients in clinical trials of indications other than acute pain. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials of oral diclofenac, meaningful elevations (i.e., more than 3 times the ULN) of AST (SGOT) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment (ALT was not measured in all studies).

In a large, open-label, controlled trial of 3,700 patients treated for 2-6 months, patients were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4%of the 3,700 patients and included marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3,700 patients. In this open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (greater than 8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis. Almost all meaningful elevations in transaminases were detected before patients became symptomatic. Abnormal tests occurred during the first 2 months of therapy with diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations.

In post marketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy, but can occur at any time during treatment with diclofenac. Post marketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

Measure transaminases (ALT and AST) periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Basedon clinical trial data and postmarketing experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. Diclofenac Sodium Injectionis not indicated for long-term treatment. However, severe hepatic reactionscan occur at any time during treatment with diclofenac.

If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), discontinue Diclofenac Sodium Injectionimmediately. To minimize the possibility that hepatic injury will become severe between transaminase measurements, inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and “flu-like”symptoms), and the appropriate action

Patients should take if these signs and symptoms appear. To minimize the potential risk for an adverse liver-related event in patients treated with diclofenac, use the lowest effective dose for the shortest duration possible. Exercise caution when prescribing Diclofenac Sodium Injectionwith concomitant drugs that are known to be potentially hepatotoxic (e.g., acetaminophen, certain antibiotics, anti-epileptics).

Hypertension

NSAIDs, including Diclofenac Sodium Injection, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Use NSAIDs, including Diclofenac Sodium Injection, with caution in patients with hypertension. Monitor blood pressure closely during the initiation of NSAID treatment and throughout the course of therapy.

Patients taking ACE inhibitors, thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs.

Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. Use Diclofenac Sodium Injectionwith caution in patients with fluid retention or heart failure.

Anaphylactic Reactions

As with other NSAIDs, anaphylactic reactions may occur in patients without known prior exposure to Diclofenac Sodium Injection. Diclofenac Sodium Injection is contraindicated in patients with the aspirintriad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs.

Serious Skin Reactions

NSAIDs, including Diclofenac Sodium Injection, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin manifestations, and discontinue Diclofenac Sodium Injectionat the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

Starting at 30 weeks gestation, Diclofenac Sodium Injectionandother NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. If this drug is used during this time period in pregnancy, the patient should be apprised of the potential hazard to a fetus.

Corticosteroid Treatment

Diclofenac Sodium Injectioncannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroidresponsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

Masking Inflammation and Fever

The pharmacological activity of Diclofenac Sodium Injectionin reducing inflammation, and possiblyfever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Hematological Effects

Anemia may occur in patients receiving NSAIDs, including Diclofenac Sodium Injection. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. In patients on long-term treatment with NSAIDs, including diclofenac, check hemoglobin

or hematocrit if they exhibit any signs or symptoms of anemia or blood loss. Diclofenac Sodium Injectionis not indicated for long-term treatment.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Carefully monitor patients who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants.

Pre-existing Asthma

Patientswith asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Sincecross-reactivity between aspirin and NSAIDs has been reported in such aspirin-sensitive patients, including bronchospasm, Diclofenac Sodium Injectionis contraindicated in patients with this form of aspirin sensitivity and should be used with caution in all patients with pre-existing asthma.

Monitoring

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, monitor for signs or symptoms of GI bleeding.

For patients on long-term treatment with NSAIDs, periodically check a CBC and chemistry profile, including liver function tests. Discontinue DiclofenacSodium Injectionif clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash), or abnormal liver tests persist or worsen. Diclofenac Sodium Injectionis not indicated for long-termtreatment.

4.5 Interaction with other medicinal products and other forms of interaction

Aspirin

When administered with aspirin, the protein binding of Diclofenac Sodium Injection is reduced. The clinical significance of this interaction is not known; however, aswith other NSAIDs, concomitant administration of Diclofenac Sodium Injection and aspirin is not generally recommended because of *the* potential of increased adverse effects.

Anticoagulants

The effects of anticoagulants (e.g., warfarin) and NSAIDs on GI bleeding are synergistic, such that the users of both drugs together have a higher risk of serious GI bleeding than users of either drug alone.

ACE Inhibitors

NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be givenconsideration in patients taking NSAIDs concomitantly with ACE inhibitors.

Cyclosporine

NSAIDs, including Diclofenac Sodium Injection, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with Diclofenac Sodium Injection may increase cyclosporine's nephrotoxicity. Use caution when Diclofenac Sodium Injection is administered concomitantly with cyclosporine.

Diuretics

Clinical studies and postmarketing observations have shown that Diclofenac Sodium Injection can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, observe patients closely for signs of renal failure, as well as to assure diuretic efficacy.

Lithium

NSAIDs have produced elevations of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance decreased by 20%. This effect has been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, observe patients carefully for signs of lithium toxicity.

Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This indicates that NSAIDs may enhance the toxicity of methotrexate. Use caution when NSAIDs are administered concomitantly with methotrexate.

CYP2C9 Inhibitors or Inducers

Diclofenac is metabolized by cytochrome P450 enzymes, predominantly by CYP2C9. Co-administration of diclofenac with CYP2C9 inhibitors (e.g. voriconazole) may enhance the exposure and toxicity of diclofenac whereas co-administration with CYP2C9 inducers (e.g. rifampin) may lead to compromised efficacy of diclofenac. Use caution when dosing Diclofenac Sodium Injection with CYP2C9 inhibitors or inducers; a dosage adjustment may be warranted.

4.6 Fertility, pregnancy and breastfeeding

Use of NSAIDs, including Diclofenac Sodium Injection, during the third trimester of pregnancy increase the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including Diclofenac Sodium Injection, in pregnant women starting at 30 weeks of gestation (third trimester).

There are no adequate and well-controlled studies of Diclofenac Sodium Injection in pregnant women. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimester of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss.

In animal reproduction studies, no evidence of teratogenicity was observed in mice, rats, and rabbits given diclofenac during the period of organogenesis at doses up to approximately 0.7,0.7, and 1.3 times, respectively, the maximun recommended human dose(MRHD) of Diclofenac Sodium Injection despite the presence of maternal and fetal toxicity at these doses [see Data]. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as diclofenac, resulted in increased pre-and post-implantation loss.

4.7 Effects on ability to drive and use machines

Diclofenac Sodium Injection may make you feel drowsy or dizzy, or cause headaches or problems with vision. If you are affected, do not drive or operate machinery.

4.8 Undesirable effects

In patients taking diclofenac or other NSAIDs, the most frequently reported adverse reactions occurring in approximately 1%-10% of patients are:

Gastrointestinal experiences including abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal) and vomiting.

Abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased

bleeding time, pruritus, rashes and tinnitus.
Additional adverse reactions reported occasionally include:
Body as a Whole: fever, infection, sepsis
Cardiovascular System: congestive heart failure, hypertension, tachycardia, syncope Digestive System: esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal bleeding, glossitis, hematemesis, hepatitis, jaundice
Hemic and Lymphatic System: ecchymosis, eosinophilia, leukopenia, melena, purpura, rectal bleeding, stomatitis, thrombocytopenia
Metabolic and Nutritional: weight changes *Nervous System*: anxiety, asthenia, confusion, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo
Respiratory System: asthma, dyspnea
*Skin and Appendages:*alopecia, photosensitivity, sweating increased
*Special Senses:*blurred vision
Urogenital System: cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, proteinuria, renal failure.
Other adverse reactions, which occur rarely are:
Body as a Whole: anaphylactic reactions, appetite changes, death
Cardiovascular System: arrhythmia, hypotension, myocardial infarction, palpitations, vasculitis
Digestive System: colitis, eructation, fulminant hepatitis with and without jaundice, liver failure,liver necrosis, pancreatitis
Hemic and Lymphatic System: agranulocytosis, hemolytic anemia, aplastic anemia,lymphadenopathy, pancytopenia
Metabolic and Nutritional: hyperglycemia
Nervous System: convulsions, coma, hallucinations, meningitis
*Respiratory System:*respiratory depression, pneumonia
*Skin and Appendages:*angioedema, toxic epidermal necrolysis, erythema multiforme, exfoliativedermatitis, Stevens-Johnson syndrome, urticaria
Special Senses: conjunctivitis, hearing impairment

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 EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may be employed but are not likely to be useful due to high protein binding.

For additional information about overdosagetreatment, consider contacting a regional poison control center.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Non-steroidal anti-inflammatory drugs (NSAIDs). ATC code M01AB.

Mechanism of action

Diclofenac Sodium Injectionis a non-steroidal agent with markedanalgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase (cyclo-oxygenase). Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis incartilage at concentrations equivalent to the concentrations reached in human beings. Whenused concomitantly with opioids for the management of post-operative pain, diclofenacsodium often reduces the need for opioids.

5.2 Pharmacokinetic properties

Following intravenous administration of Diclofenac Sodium Injectionto healthy volunteers, plasma concentrations of diclofenac exceed that of immediate-release oral diclofenac for the first 45 minutes reaching a maximum of 4.8-fold 5 minutes after administration.
The pharmacokinetics of diclofenac following intravenous administration of Diclofenac Sodium Injectionand oral doses of immediate-release diclofenac are compared in Table 1.

Table 1: Single-dose and Multiple-dose Pharmacokinetics ofDiclofenac Sodium Injection and Oral Immediate Release (IR) Diclofenac Potassium

Parameter[1]	Dyloject 37.5 mg IV	Oral IR Diclofenac 50 mg PO
Single Dose		
C_{max} (ng/mL)	6,031 ± 1,178	1,246 ±732
T_{max} (h)	0.083	1.5
$AUC_{(inf)}$ (h·ng/mL)	1,859 ± 376	1,562 ± 519
$t_{1/2}$ (h)	1.44 ± 0.27	1.28 ± 0.27
CL (mL/min)	324 ± 63.0	526 ± 179
V_z (L)	40.1 ± 9.77	57.3 ± 20.4
Multiple Dose		
C_{max} (ng/mL)	5,617 ± 1,799	851 ± 462
T_{max} (h)	0.083	1.49
$AUC_{(0-t)}$ (h·ng/mL)	1,839 ± 506	1,350 ± 601
$t_{1/2}$ (h)	2.29 ± 0.63	2.80 ± 0.66
CL (mL/min)	387 ± 394	894 ± 1,392
V_z (L)	83.4 ± 127	242 ± 486

IV=intravenous; PO=oral; [1]CL and V_z are CL/F and V_z/F for oral immediate release diclofenac

Diclofenac Sodium Injection administered as an intravenous bolus dose of 37.5 mg every 6 hours for 4 doses to healthy subjects (N=36) showed minimal accumulation with mean values for Cmaxand AUC equivalent between the first and the fourth dose.

Diclofenac Sodium Injection exhibits linear pharmacokinetics over intravenous doses ranging from 18.75 to 75 mg and injection times ranging from a bolus (less than 5 seconds) to 60 seconds.

Distribution

Following administration of Diclofenac Sodium Injection, the apparent volume of distribution during the terminal elimination phase (Vz) of diclofenac is 40.1 ±9.77 L.

Diclofenac is more than 99% bound to human serum proteins, primarily albumin. Serum binding is constant over the concentration range (0.15-105 mcg/mL) achieved with the recommended doses.

Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovialfluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

HPβCD is distributed in the extracellular fluids following administration of Diclofenac Sodium Injection, and hasa volume of distribution during the terminal elimination phase (Vz) of 21.8 ±7.36 L.

Metabolism

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-hydroxydiclofenac were approximately 50% and 4% of the parent compound after single oral dosing compared to 27% and 1% in normal healthy subjects.

Excretion

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites.

Plasma concentrations of Diclofenac Sodium Injectiondecline from peak levels in a biexponential fashion, with a terminal phase half-life of approximately 1.4 hours following intravenous administration.

Total systemic clearance of diclofenac in plasma following administration of Diclofenac Sodium Injectionis 324 ± 63 mL/min.

Little or no free unchanged diclofenac is excreted in the urine following administration of Diclofenac Sodium Injection. Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites. Less than 1% is excreted as unchanged substance.

The terminal half-life of HPβCD in plasma following administration of Diclofenac Sodium Injectionis approximately 2.7 ± 1.4 hours.

Special Populations

Age

*Pediatric:*The pharmacokinetics of Diclofenac Sodium Injectionhave not been established in pediatric subjects.

Geriatrics: The effect of aging on the pharmacokinetics of Diclofenac Sodium Injectionwas studied in 88 subjects from 18 to 86 years old. The terminal half-life for subjects aged 65 to 74 years was1.4 hours and for subjects greater than or equal to 75 years was 2.1 hours. Clearance of diclofenac following administration of Diclofenac Sodium Injectionwas not affected by age.

Race: Pharmacokinetics of diclofenac following injection of Diclofenac Sodium Injectionwas studied in Caucasian, Black/African and Asian subjects. After taking body weight into account there was no difference in pharmacokinetics of diclofenac with respect to race.

*Gender:*Systemic exposure of diclofenac was 30% higher in females compared to males following Diclofenac Sodium Injectionadministration. However, this is possibly due to the effect of body weight on clearance of diclofenac. After taking body weight into account there was no difference in pharmacokinetics of diclofenacwith respect to gender.

Hepatic Insufficiency

The pharmacokinetics of Diclofenac Sodium Injectionwere evaluated in 8 subjects with mild hepatic impairment (Child-Pugh Classification A, Score of 5 to 6 and a bilirubin of less than or equal to 2.5 mg/dL) compared to matched healthy subjects. The pharmacokinetics of diclofenac following administration of Diclofenac Sodium Injectionin mild hepatic impaired subjects were not altered. Pharmacokinetics of Diclofenac Sodium Injectionhas not been evaluated in moderate or severe hepatic impaired subjects.

Renal Insufficiency

The pharmacokinetics of Diclofenac Sodium Injectionin mild (n = 8), and moderate (n = 5) renal impaired subjects were not significantly altered compared to healthy subjects (n = 7).

Effect of Body Weight

Pharmacokinetics of diclofenac following Diclofenac Sodium Injectionappear to be dependent on body weight. The pharmacokinetics of Diclofenac Sodium Injectionwere studied in 88 subjects ranging in weight from 53 to156.2 kg. Clearance of diclofenac in subjects weighing below 95 kg is 282±68 mL/min compared to 356±53 mL/min in subjects above 95 kg body weight (approximately 30% higher clearance). The volume of distribution increased with increased body weight and the proportional increase in clearance resulted in no change in elimination half-life with increased body weight.

5.3 Preclinical safety data

Nonclinical data on diclofenac, HPβCD and their combination in Diclofenac Sodium Injection revealed nospecial hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction, and localtolerance studies with the following provisions for potential gastrointestinal toxicity andfoetal risk of premature closure of the ductus arteriosus in late pregnancy.

A single oral dose of 0.1 mg/kg of diclofenac to pregnant rats on pregnancy day 21 caused a constriction of the ductus arteriosus in the offspring, a known effect of prostaglandin-inhibiting drugs. Administration of diclofenac in late pregnancy is therefore not recommended.

In the 4-week IV toxicity studies conducted with diclofenac in rats (3, 7 and 15 mg/kg/day)and diclofenac and HPβCD in monkeys (3, 15 and 60 mg/kg/day and 533 mg/kg/dayrespectively) observed effects were essentially similar for both species and were allconsidered expected. Diclofenac induced a low incidence of mortality/premature sacrifice (due to peritonitis), gastrointestinal toxicity and regenerative anaemia in rats at a dose level of 15 mg/kg/day. Recovery was complete after a 9-week treatment-free period.

In monkeys, diclofenac caused gastrointestinal toxicity, regenerative anaemia andexacerbation of minor tail skin lesions at dose levels of 15 and 60 mg/kg/day. Resolution ofthese findings could not be assessed in the 60 mg/kg/day dose group, due to prematuresacrifice. Findings attributed to HPβCD included very mild to mild renal tubularvacuolization in rats and very mild to mild granular appearance of the renal tubular cells inthe medullar rays in monkeys. Following a relatively long treatment-free period ascompared to the duration of treatment, partial and complete recovery of HPβCD-associatedfindings has been demonstrated in rats and monkeys, respectively.

The No Adverse Effect Level for HPβCD-related effects after 4 weeks of administration islower than 26.6 mg HPβCD/kg/day in both species.

The solubilising agent HPβCD has been found to produce pancreatic hyperplasia andneoplasia when administered orally to rats at doses of 500, 2000 or 5000 mg/kg per day for25 months. Adenocarcinomas of the exocrine pancreas produced in the treated animalswere not seen in the untreated group and are not reported in the historical controls. Thesefindings were not observed in the mouse carcinogenicity study, nor in a 12-month toxicitystudy in dogs or in a 2-year toxicity study in female cynomolgous monkeys.

In the Diclofenac Sodium Injection nonclinical studies diclofenac and HPβCD alone and in combination were not mutagenic or clastogenic. Diclofenac has shown no carcinogenic potential. The adenocarcinomas observed in the exocrine pancreas in the 2-year oral carcinogenicity study with HPβCD in rats were not considered a clinical hazard for Diclofenac Sodium Injection because HPβCD is not genotoxic. Diclofenac Sodium Injection is intended for short-term treatment only, and no pancreatotrophic changes were observed in the 4 week intravenous studies in rats and monkeys described above.

6. Pharmaceutical particulars

6.1 List of excipients

Lidocaine Hydrochloride,

1, 2-Propylene Glycol

Polyethylene Glycol-400

Sodium Sulfite, EDTA-2Na

Water for Injections.

6.2 Incompatibilities

In the absence of compatibility studies, this pharmaceutical product must not bemixed with other pharmaceutical products.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in tightly closed containers, at Controlled Room Temperature 20 to 25℃.

Do not freeze. Protect from light.

6.5 Nature and contents of container

2ml, Type I brown ampoule, 10 ampoules or 10*10 ampoules packed in a box.

6.6 Special precautions for disposal and other handling

-Keep Diclofenac Sodium Injection out of reach and sight of children.
-Not made with natural rubber latex.
-Please do not use if the primary package is broken.

7. Marketing authorization holder

Cisen Pharmaceauticals co., ltd
Tongji Tech-Industrial Garden, Jining High&New
Technology Industries Development Zone,
Jining, Shandong Province,
P.R. China

8. Authorization number

Registration No: 05898/07150/NMR/2019

9. Date of authorization

Approval date: 28-04-2021

10. Date of revision of the text

October 2022