New Zealand Data Sheet

APO-DICLO SR

1. PRODUCT NAME

Apo-Diclo SR 75mg modified release tablet

Apo-Diclo SR 100mg modified release tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 75mg diclofenac sodium and typically weigh 195 to 207mg.
Each tablet contains 100mg diclofenac sodium and typically weigh 258 to 277mg.

Excipient with known effect
Apo-Diclo SR is gluten and lactose free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

APO-DICLO SR 75mg tablet are light pink, triangular biconvex, bevelled-edge, film coated tablet. Engraved “APO” over “75” on one side, other side plain.

APO-DICLO SR 100 mg tablets are pink, round biconvex, bevelled-edge, film-coated tablet. Engraved “APO” over “100” on one side, other side plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of:

- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondylarthritis, painful syndromes of the vertebral column, nonarticular rheumatism.
- Post-traumatic and post-operative pain, inflammation, and swelling, e.g. following dental or orthopaedic surgery.
- Painful and/or inflammatory conditions in gynaecology, e.g. primary dysmenorrhoea or adnexitis.

4.2 Dose and method of administration

This product is not able to deliver all approved dose regimens.

Diclofenac slow release tablet should only be prescribed when the benefits are considered to outweigh the potential risks. After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4 Special Warnings and Precautions for use).

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

Dose

General population

The recommended initial daily dose is 100 to 150mg, in 1 or 2 divided doses.

In milder cases, as well as for long-term therapy, 75 to 100 mg daily is usually sufficient.

Where the symptoms are most pronounced during the night or in the morning, diclofenac slow release tablets 75mg and 100mg should preferably be taken in the evening.

Special populations

Paediatric population

Because of their dosage strength, diclofenac slow release tablets 75mg and 100mg are not suitable for children and adolescents.

Geriatrics population (Patients aged 65 or above)

No adjustments of the starting dose is generally required for elderly patients. However, caution is indicated on basic medical grounds, especially for frail elderly patients or those with low body weight (see section 4.4 Special Warnings and Precautions for use).

Patients with established cardiovascular disease or significant cardiovascular risk factors

Treatment with diclofenac slow release tablets is generally not recommended in patients with established cardiovascular disease or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular disease should be treated with diclofenac slow release tablet only after careful consideration and only at doses ≤100mg daily if treated for more than 4 weeks (see section 4.4 Special Warnings and Precaution for Use).

Patients with renal impairment

Diclofenac slow release tablets 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 administrating diclofenac to patients with renal impairment (see section 4.4 Special Warning and precaution for use section).

Patients with hepatic impairment

Diclofenac 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 administrating diclofenac slow release tablet to patients with mild to moderate hepatic impairment (see section 4.4 Special Warning and precaution for use).

Method of administration

Diclofenac SR tablets should preferably be taken before meals. The tablets should be swallowed whole with liquid and must not be divided or chewed.

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients (see section 6.1 List of excipients)
- Active gastric or intestinal ulcer, bleeding or perforation.
- Last trimester of pregnancy (see section 4.6 Fertility, pregnancy and lactation)
- Hepatic failure.
- Renal failure (GFR <15mL/min/min/1.73m^2)
- Severe cardiac failure (see section 4.4 Special warning and precaution for use)
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac SR tablet is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.

4.4 Special warnings and precautions for use

General
Patients on long-term treatment should be reviewed regularly with regards to efficacy, adverse effects, the development of risk factors and the on-going need for therapy. Consideration should be given to monitoring blood pressure, haemoglobin levels and renal functions.

Cardiovascular Thrombotic Events
Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk.

Patients with previous myocardial infarction (within the last 6 to 12 months) should not use diclofenac. Treatment with diclofenac is generally not recommended in patients with established cardiovascular disease (e.g. congestive heart failure, established ischaemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking) should be treated with diclofenac only after careful consideration and only at doses ≤100mg daily when treatment continues for more than 4 weeks.

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 (see section 4.2 Dose and Method of Administration). The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when treatment continues for more than 4 weeks.

Prescribers should inform the individual patient of the possible increased risk when prescribing diclofenac for patients at the high risk of cardiovascular events.

Physicians and patients should remain alert for such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of cardiovascular toxicity and the steps to take should they occur.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 warning. Patients should be instructed to see a physician immediately in case of such an event.

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Hypertension
NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart failure
Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore, caution is advised in patients with fluid retention or heart failure.

Gastrointestinal effects
Gastrointestinal bleeding, ulceration or perforation, which may increase with dose or duration of use and which can be fatal, have been reported with all NSAIDs, including diclofenac, and may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occur in patients receiving diclofenac , the medicinal product should be discontinued.

Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur approximately 1% of patients treated for 3-6 months and in about 2-4% patents treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Voltaren in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.8). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly.

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

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

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding,

such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors (see section 4.5).

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see section 4.8).

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal toxicity.

Doctors should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

Severe Skin Reactions
Serious skin reactions, some of them fatal including exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported very rarely in association with the use of NSAIDs, including diclofenac (see section4.8 Undesirable effects). These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash, mucosal lesions or any sign of hypersensitivity, diclofenac slow release tablet should be discontinued.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug.

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

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

Hepatic effects
Close medical surveillance is required when prescribing diclofenac to patients with impaired hepatic function, as their condition may be exacerbated.

As with other NSAIDS, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac slow release tablet, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), diclofenac slow release tablet should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

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

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

Haematological effects
During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.
Like other NSAIDs, diclofenac may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

Geriatric patients
Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight (see section 4.2 Dose and method of administration).

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

4.5 Interaction with other medicines and other forms of interaction

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

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

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

Diuretics and antihypertensive agents
Like other NSAIDS, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be

administrated with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity (see section 4.4 Special Warning and Precautions for use).

Other NSAIDs and corticosteroids
Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section 4.4 Special Warning and Precaution for use).

Anticoagulants and anti-platelet agents
Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4 Special warning and precaution for use). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs)
Concomitant administration of systemic NSAIDs, including diclofenac slow release tablets, and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4 Special Warnings and Precautions for use).

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

There have also been isolated reports of metabolic acidosis when diclofenac was co-administrated with metformin, especially in patients with pre-existing renal impairment.

Methotrexate
Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

Cyclosporin and Tacrolimus
Diclofenac, like other NSAIDs, may increase the nephrotoxicity of cyclosporin and tacrolimus due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving cyclosporin or tacrolimus.

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

Quinolone antibacterials
There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

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

CYP2C9 inducers
Caution is recommended when co-prescribing diclofenac with CYO2C9 inducers (such as rifampicin), which could result in a significant decrease in plasma concentration and exposure to diclofenac.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy

There are insufficient data on the use of diclofenac in pregnant women. Therefore, Voltaren should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the foetus. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia, fetal renal impairment with subsequent oligohydramnios and/or premature closure of the ductus arteriosus (see section 4.3 and 5.3).

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo/ fetal development. Some data from epidemiological studies suggest an increased risk of miscarriage after use of a prostaglandin synthesis inhibitor (such as NSAIDS) in early pregnancy, however the overall data from the available studies is inconclusive. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in pre- and post-implantation loss. During the first and second trimester of the pregnancy, Apo-Diclo SR should not be given unless clearly necessary. If Apo-Diclo SR is used by a woman attempting to conceive, or during the first and second trimester of the pregnancy, the dose should be kept as low as possible and the duration of the treatment as short as possible.

Breastfeeding

Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, diclofenac should not be administrated during breast feeding in order to avoid adverse effects in the infant.

Fertility

As with other NASIDs, the use of diclofenac may impair female fertility and is not recommended in women attempting to conceive. In women who 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 from clinical trials and/or spontaneous or literature reports (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (>1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000).

The following undesirable effects include those reported with diclofenac SR and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Table 1 Adverse drug reactions

Blood and lymphatic system disorders	
Very rare:	Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.
Immune system disorders	
Rare:	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare:	Angioedema (including face oedema).
Psychiatric disorders	
Very rare:	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common:	Headache, dizziness.
Rare:	Somnolence.
Very rare:	Paraesthesia, memory impairment, convulsion, anxiety, tremor, meningitis aseptic, dysgeusia, cerebrovascular accident.
Eye disorders	
Very rare:	Visual impairment, blurred vision, diplopia.
Ear and labyrinth disorders	
Common:	Vertigo.
Very rare:	Tinnitus, impaired hearing

Cardiac disorders	
Uncommon*:	Myocardial infarction, cardiac failure, palpitations, chest pain.
Frequency unknown:	Kounis syndrome
Vascular disorders	
Very rare:	Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare:	Asthma (including dyspnoea).
Very rare:	Pneumonitis.
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, decreased appetite.
Rare:	Gastritis, gastrointestinal haemorrhage, haematemesis, melaena, haemorrhagic diarrhoea, gastrointestinal ulcer (with or without bleeding gastrointestinal stenosis or perforation which may lead to peritonitis).
Very rare:	Colitis (including haemorrhagic colitis, ischemic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, intestinal diaphragm disease, pancreatitis, haemorrhoids aggravated.
Hepatobiliary disorders	
Common:	Transaminases increased.
Rare:	Hepatitis, jaundice, liver disorder.
Very rare:	Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common:	Rash.
Rare:	Urticaria.
Very rare:	Bullous dermatitis, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, photosensitivity reaction, Henoch-Schonlein purpura, pruritus.
Renal and urinary disorders	
Very rare:	Acute kidney injury (acute renal failure), haematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare:	Oedema.

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

Description of selected adverse drug reactions

Arteriothrombotic events
Meta-analysis and pharmacoepidemiological data point towards a small 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 4.4 Special Warning and Precautions for use).

Visual effects
Visual disturbances such as visual impairment, blurred vision or diplopia appear to be NSAID class effects and are usually reversible on discontinuation. A likely mechanism for the visual disturbances is the inhibition of prostaglandin synthesis and other related compounds that alter the regulation of retinal blood flow resulting in potential changes in vision. If such symptoms occur during diclofenac treatment, an ophthalmological examination may be considered to exclude other causes.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professional are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage is possible.

Therapeutic measures

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 haemoperfusion 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

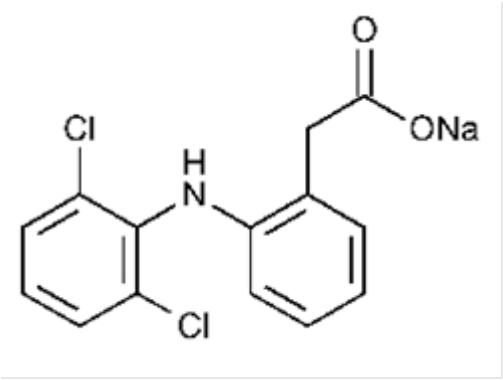
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group ATC: Anti-inflammatory and antirheumatic products, non steroids, acetic acid derivatives and related substances.

ATC code: M01A B05

Chemical Structure:



Mechanism of actions

Apo-Diclo SR contains diclofenac sodium, a non-steroidal compound with pronounced anti-rheumatic, anti-inflammatory, analgesic and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain and fever.

Diclofenac sodium *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to those reached in humans.

Pharmacodynamic effects

In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac elicit a clinical response characterised by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function,

In post-traumatic and post-operative inflammatory conditions, diclofenac rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema.

Apo-Diclo SR 75mg tablets are particularly suitable for patients in whom a daily dose of 75mg or 100mg is appropriate to the clinical picture. The possibility of prescribing the medicinal product in a single daily dose considerably simplifies long-term treatment and helps to avoid the possibility of dosage errors. Apo-Diclo SR 75mg tablets also allow the maximum daily dose of 150mg to be given in a balanced b.i.d schedule.

5.2 Pharmacokinetic properties

Absorption

Judged by urinary recovery of unchanged diclofenac and it hydroxylated metabolites, the same amount of diclofenac is released and absorbed from diclofenac slow release tablets

as from gastro-resistant tablets. However, the systemic availability of diclofenac from diclofenac slow release tablets is on average about 82% of that achieved with the same dose of diclofenac administrated in the form of gastro-resistant tablets (possibly due to release-rate dependent "first-pass" metabolism). As a result of a slower release of the active substance from diclofenac slow release tablets, peak concentrations attained are lower than those observed following the administration of gastro-resistant tablets.

Mean peak concentrations of 0.5 micrograms/mL or 0.4 micrograms/mL (1.6 or 1.25 micromol/L) are reached on average 4 hours after ingestion of prolonged-release tablet of 100mg or 75mg.

Food has no clinically relevant influence on the absorption and systemic availability of diclofenac slow release tablets.

On the other hand, mean plasma concentrations of 13ng/mL (40 nmol/L) can be recorded at 24 hours (16 hours) after administration of diclofenac slow release tablets 100mg (75mg). Since about half of diclofenac is metabolised during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) following oral or rectal administration is about half that following an equivalent parenteral dose.

Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

Trough concentrations are around 22 ng/mL or 25 ng/mL (70 nmol/L or 80 nmol/L) during treatment with diclofenac slow release tablets 100mg once daily or 75mg twice daily.

Distribution
99.7% of diclofenac is bound to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution calculated is 0.12 to 0.17 L/kg.

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma values, concentrations of the active substance are already higher in the synovial fluid than in the plasma, and they remain higher for up to 12 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.

Metabolism
Biotransformation of diclofenac takes place partly by glucuronidation in the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-,4'-hydroxy-,5-hydroxy,4',5-dihyroxy- and 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much smaller extent than diclofenac.

Elimination
Total systemic clearance of diclofenac from plasma is 263 ±56 mL/min (mean value ±SD). The terminal half-life in plasma is 1 to 2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 3 hours. One metabolite, 3'-hydroxy-

4'-methoxy-diclofenac has a much longer plasma half-life. However, this metabolite is virtually inactive.

About 60% of the administered dose is excreted in the urine as the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Linearity/non-linearity
The amount absorbed is linearly related to the size of the dose.

Pharmacokinetics in special patient groups
No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed.

In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of <10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

5.3 Preclinical safety data

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. In standard preclinical animal studies, there was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.

Diclofenac had no influence on the fertility of parent animals in rats. Except for minimal fetal effects at maternally toxic doses, the prenatal, perinatal and postnatal development of the offspring was not affected.

Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the ductus arteriosus in the pregnant rat. Maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation in rats. The slight effects of diclofenac on reproduction parameters and delivery as well as constriction of the ductus arteriosus in utero are pharmacologic consequences of this class of prostaglandin synthesis inhibitors (see section 4.3 Contraindications section 4.6 Fertility, pregnancy and breastfeeding).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Apo-Diclo SR tablet contains the following excipients:

- Microcrystalline cellulose
- Hyetellose

- Dextrates
- Magnesium stearate
- Hypromellose
- Iron oxide red
- *Iron oxide yellow
- Macrogol 3350
- Titanium dioxide
- Carnauba wax

*For Apo-Diclo SR 100mg only.

6.2 Incompatibilities

Nil

6.3 Shelf life

36 months from date of manufacture

6.4 Special Precautions for storage

Store at or below 30°C

Protect from heat, light and moisture.

6.5 Nature and contents of container

APO-DICLO SR 75mg and 100mg in HDPE bottles containing 100, 500 and 1000 tablets

APO-DICLO SR 75mg and 100mg: PVC/PVdC/Al or PVC/PE/PVdC/Al blisters containing 30, 60, 90, 100, 500 and 1000 tablets.

Not all strengths and pack sizes may abe marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Apotex NZ Ltd.
32 Hillside Road
Wairau Valley
AUCKLAND 0627

Telephone: (09) 444 2073
Fax: (09) 444 2951
E-mail: NZcustomerservice@apotex.com

9. DATE OF FIRST APPROVAL

Apo-DICLO SR 75mg tablets date of first approval: 24 Jun 1999
Apo-DICLO SR 100mg tablets date of first approval: 22 Oct 1998

10. DATE OF REVISION OF THE TEXT

21 November 2018

Summary Table of Changes

Section changed	Summary of new information
Whole data sheet	Information updated to align with latest registered and approved information.
3	Updated as per approved and registered drug product description. Minor editorial change.