SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diclo-XL 100

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Diclofenac Sodium Ph. Eur. 100mg.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White, circular, biconvex, modified release tablets engraved with CX58 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the management of chronic conditions, such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

4.2 Posology and method of administration

Adults: The usual dosage is 100mg (one tablet) daily, taken whole with liquid, preferably with or after food.

Elderly: The elderly are at increased risk of the serious consequences of adverse reactions. If Diclo-XL 100 is considered necessary the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

Children: Diclo-XL 100 tablets are not recommended for use in

Children.

For oral use only.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4 Special warnings and precautions for use).

4.3 Contraindications

Hypersensitivity to diclofenac or any of the excipients.

Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti- inflammatory drugs.

Severe heart failure, hepatic failure and renal failure (see section

4.4). During the last trimester of pregnancy (see section 4.6).

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

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

The use of Diclofenac with concomitant 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 Interactions with other medicaments and other forms of interaction).

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal (see section 4.2). 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 Posology and Method of administration).

As with other nonsteroidal anti-inflammatory drugs including diclofenac, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug (see section 4.8 Undesirable effects).

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

Respiratory disorders:
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. Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Cardiovascular, Renal and Hepatic Impairment:
The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3). Discontinuation therapy is usually followed by recovery to the pre-treatment state.

Hepatic effects:
Close medical surveillance is required when prescribing diclofenac to patients with impairment of 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, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), diclofenac should be discontinued. Hepatitis may occur with diclofenac without prodromal symptoms. Caution is called for when using diclofenac in patients with hepatic porphyria, since it may trigger an attack.

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

Clinical trial and epidemiological data consistently point towards increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (l50mg daily) and in long term treatment.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration.

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Gastrointestinal bleeding, ulceration and perforation:

Gastrointestinal bleeding (haematemesis, melaena), ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3) and in the elderly. These patients should commence treatment and be maintained on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding), particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anti-coagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

When gastrointestinal bleeding or ulceration occurs in patients receiving Diclofenac, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal; disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

An increased risk of anastomotic dehiscence has been noted in patients receiving oral diclofenac for analgesia after colon resection surgery.

Haematological effects:
During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended. Diclofenac may reversibly inhibit platelet aggregation (see anticoagulants in section 4.5 Interaction with other medicinal products and other forms of interactions). Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

SLE and mixed connective tissue disease:
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

Dermatologic al:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk for 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. Diclofenac should be discontinued at the first appearance of skin rash, mucosal lesions or other signs of hypersensitivity.

Porphyr ia
Diclofenac should only be used with extreme caution in patients with porphyria where no suitable alternative is available.

Impaired female fertility:
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 (see section 4.6).

Excipie nts
Contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Diclofenac is bound practically completely to plasma albumin (99.7%) and consequently displacement reactions with high protein binding affinity must be borne in mind.

Care should be taken in patients treated with any of the following drugs as interactions have been reported in some patients.

Anti-hypertensives: reduced anti-hypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, hence serum potassium should be monitored. Therefore, the combination should be administered 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 periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

Cardiac Glycosides e.g. digoxin: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels. Monitoring of the serum digoxin level is recommended.

Lithium: Decreased elimination of lithium. Monitoring of the serum lithium level is recommended.

Methotrexate: Decreased elimination of methotrexate. Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increase. Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.
Ciclosporin: Increased risk of nephrotoxicity 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 ciclosporin.

Mifepristone: NSAIDs should not be used 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4).

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4). Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Diclofenac in a high dose can reversibly inhibit platelet aggregation. Increased risk of gastrointestinal bleeding (see section 4.4).

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions. This may occur in patients with or without a previous history of epilepsy or convulsions.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostaglandin effects of both NSAID and calcineurin inhibitor.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Drugs known to cause hyperkalaemia: Concomitant treatment with potassium□sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently.

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

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 hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason,

monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

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

4.6 Pregnancy and lactation

Pregnanc
y:
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.

Diclofenac should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

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.

Lactatio
n:
In the limited studies so far available, NSAIDs can appears in the breast milk in very low concentrations. NSAIDs should, if possible, be avoided in breastfeeding in order to avoid undesirable effects in the infant (see section 5.2 Pharmacokinetic properties).

Female 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. See also section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

Dizziness, drowsiness, fatigue, visual disturbances or headaches are possible undesirable effects after taking NSAIDs, if affected the patients should not drive or operate machinery.

4.8 Undesirable Effects

Adverse reactions are ranked under the heading of frequency, the most frequent first, using the following convention: very common: (>1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000); not known: cannot be estimated from available data.
The following undesirable effects include those reported with other short-term or long-term use.

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leucopoenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.
Immune system disorders	
Rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare	Angioneurotic oedema (including face oedema).
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common	Headache, dizziness.
Rare	Somnolence, tiredness.
Very rare	Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.
Unknown	Confusion, hallucinations, disturbances of sensation, malaise.

Eye disorders	
Very rare	Visual disturbance, vision blurred, diplopia.
Unknown	Optic neuritis.
Ear and labyrinth disorders	
Common	Vertigo.
Very rare	Tinnitus, hearing impaired.
Cardiac disorders	
Very rare	Palpitations, chest pain, cardiac failure, myocardial infarction.
Vascular disorders	
Very rare	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare	Asthma (including dyspnoea).
Very rare	Pneumonitis.
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare	Gastritis, gastrointestinal haemorrhage, haematemesis, haemorrhagic diarrhoea, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly).
Very rare	Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.
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 eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.
Renal and urinary disorders	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare	Oedema
Reproductive system and breast disorders	
Very rare	Impotence.

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 (150mg daily) and in long term treatment. (see section 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use).

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

a) Symptoms
Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting and occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

B) Therapeutic measures
Patients should be treated symptomatically as required.
Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.
Good urine output should be ensured.
Renal and liver function should be closely monitored.
Patients should be observed for at least four hours after ingestion of potentially toxic amounts.
Frequent or prolonged convulsions should be treated with intravenous diazepam.
Other measures may be indicated by the patient's clinical condition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The exact mechanism of action of diclofenac has not been clearly established,
But many of the actions appear to be associated principally with the inhibition of prostaglandin synthesis. Diclofenac inhibits the synthesis of prostaglandins in body tissue by inhibiting cyclooxygenase, an enzyme that catalyses formation of prostaglandin precursors (endoperoxides) from arachidonic acid.

5.2 Pharmacokinetic properties

After ingestion of the diclofenac slow release tablet, the active principle is slowly released into the gastrointestinal contents. Once released from the tablet, diclofenac is rapidly absorbed from the gastrointestinal tract but is subject to first pass metabolism. Peak plasma concentrations occur about 6-8 hours after administration of the sustained release tablets when taken with a meal. Food and antacids decrease the rate but not the extent of absorption of diclofenac. The active substance is 99.7% bound to plasma proteins, mainly albumin. Diclofenac enters the synovial fluid and peak synovial fluid concentrations at steady state exceed plasma concentrations. Furthermore, elimination from the synovial fluid is slower than from plasma. Diclofenac and its metabolites cross the placenta and traces of diclofenac have been found in the milk of lactating woman. The half-life for the terminal elimination phase is 1-2 hours. Approximately 60% of the administered dose is excreted via the kidneys in the form of metabolites and less than 1% in unchanged form. About 30% of the dose is excreted via the bile in metabolised form. In patients with impaired renal function, accumulation of diclofenac sodium has not been reported. However, half-life of diclofenac may be prolonged in patients with severe renal treatment.

5.3 Preclinical safety data

Multiple dose studies were performed in rats, dogs, and monkeys. At toxic doses there were gastro-intestinal ulcers and disorders in the blood picture in all species. Genetic toxicology studies with diclofenac sodium show that diclofenac is not a mutagen. Carcinogenicity studies have been conducted in mice and rats. No carcinogenic effect has been seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Magnesium Stearate
Hydrogenated Vegetable Oil Type I USNF
(Sterotex)
Povidone K30
Talc

6.2 Incompatibilities

None Known.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store between 15^{o}C and 25^{o}C in a dry place.

6.5 Nature and contents of container

Blister packs(Aluminium/polyvinylchloride): 20,21,28,30 tablets
Polypropylene bottles with low-density polyethylene caps: 56,100,250 & 500 tablets
High-density polyethylene bottles with low-density polyethylene screw caps: 56,100,250 & 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not relevant

7. MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd
Unit 4 Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD18 9SS
Trading as: Co-pharma

8 MARKETING AUTHORISATION NUMBER(S)

PL 13606/0144

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/02/2009

10 DATE OF REVISION OF THE TEXT

27/04/2017