

**DICLOFENAC POTASSIUM 12.5 MG TABLETS
PL 24668/0001**

UKPAR

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**DICLOFENAC POTASSIUM 12.5 MG TABLETS
PL 24668/0001**

LAY SUMMARY

The MHRA granted Caduceus Pharma Limited a Marketing Authorisation (licence) for the medicinal product Diclofenac potassium 12.5mg tablets (PL 24668/0001). This is a prescription only medicine (POM) for the relief of symptoms of inflammation and pain.

Diclofenac potassium 12.5mg tablets contain the active ingredient diclofenac potassium which is a non-steroidal anti-inflammatory drug (NSAID).

The test product was considered to be the same as Voltarol Dolo 12.5mg tablets which was used in the bioequivalence study instead of the higher strength reference products Voltarol Rapid 25mg and 50mg tablets.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Diclofenac potassium 12.5mg tablets outweigh the risks, hence a Marketing Authorisation has been granted.

**DICLOFENAC POTASSIUM 12.5 MG TABLETS
PL 24668/0001**

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Diclofenac potassium 12.5mg tablets (PL 24668/0001) to Caduceus Pharma Limited on 18 December 2006. The product is a prescription only medicine.

The application was submitted as an abridged application according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to the original products, Voltarol Rapid 25mg and 50mg tablets.

The product contains the active ingredient diclofenac potassium and is indicated for rheumatoid arthritis, osteoarthritis, low back pain, migraine attacks; acute musculo-skeletal disorders and trauma such as peri-arthritis, tendonitis, tenosynovitis, bursitis, relief of pain in fractures, sprains, strains and dislocations; ankylosing spondylitis; acute gout; control of pain and inflammation in orthopaedic, dental and other minor surgery; and pyrophosphate arthropathy and associated disorders.

Diclofenac potassium is an NSAID. It prevents the bio-synthesis of prostaglandin and regulates arachidonic acid release and uptake.

The application for Diclofenac potassium 12.5mg tablets depends on the bioequivalence study that compares the applicant's product with Voltarol Dolo 12.5mg tablets instead of the higher strength Voltarol Rapid 25mg and 50mg tablets.

PHARMACEUTICAL ASSESSMENT

COMPOSITION

The product is formulated as a film-coated tablet containing the active pharmaceutical ingredient diclofenac potassium at a strength of 12.5mg. The excipients present are silica colloidal anhydrous, sodium starch glycollate, povidone, starch maize, calcium hydrogen phosphate anhydrous and magnesium stearate. In addition, polyvinyl alcohol partially hydrolysed, titanium dioxide, talc, lecithin soya and xanthium gum are present in the film coating.

The tablets are presented in aluminium-foil sealed PVC/PVdC blisters, in packs of 7, 10, 14, 28, 30, 50, 56, 98 and 100 tablets.

DRUG SUBSTANCE

Diclofenac potassium

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the Ph Eur specification is provided for diclofenac potassium.

Analytical methods have been validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

Diclofenac potassium is stored in appropriate packaging.

Stability data have been generated supporting a retest period of 5 years when stored in the proposed packaging.

DRUG PRODUCT

Other ingredients

All excipients used in the manufacture of the tablets are routinely tested for compliance with current relevant international standards.

Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin.

Dissolution profiles

Dissolution profiles for the drug product were found to be similar to the originator products marketed in various European countries. The data demonstrate that the dissolution specification is acceptable.

Manufacture

A full description and a detailed flow-chart of the manufacturing method including in-process control steps has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Satisfactory process validation has been carried out.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

Finished product specification

The proposed finished product specification is acceptable and the analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed release specification.

Container Closure System

Satisfactory specifications and certificates of analysis have been provided for the packaging components.

Stability

Finished product stability data support the proposed shelf-life of 36 months with storage conditions of 'Do not store above 25°C'.

Bioequivalence/bioavailability

Satisfactory certificates of analysis have been provided for the test and reference batches.

SPC, PIL and Labels

The SPC, PIL and labels are pharmaceutically acceptable.

CONCLUSION

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution profiles have been demonstrated for the proposed and reference products.

It is recommended that a Marketing Authorisation should be granted for this application.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

This is a generic abridged application for film-coated tablets containing 12.5mg diclofenac potassium.

The application is submitted under the provisions of Directive 2001/83/EC Article 10.1(a)(iii), claiming that the product is essentially similar to the proprietary products Voltarol Rapid 25 and 50mg which were authorised in the UK. Because these products are at a higher strength, Voltarol Dolo 12.5mg tablets sourced from Germany were used in the bioequivalence study submitted as part of this application. It is legally acceptable for the reference product used in the bioequivalence study to be licensed in another member state.

INDICATIONS

The proposed indications are:

- Rheumatoid arthritis
- Osteoarthritis
- Low back pain
- Migraine attacks
- Acute musculo-skeletal disorders and trauma such as peri-arthritis (especially frozen shoulder), tendinitis, tenosynovitis, bursitis, sprains, strains and dislocations; relief of pain in fractures
- Ankylosing spondylitis
- Acute gout
- Control of pain and inflammation in orthopaedic, dental and other minor surgery
- Pyrophosphate arthropathy and associated disorders

These are considered satisfactory and to be fully consistent with the SPC for Votarol Rapid 25mg and 50mg tablets.

DOSE AND DOSE SCHEDULE

The proposed dose and dose schedule for this product to be used for the above indications ranges from 50mg to 200mg daily and is the same as for Votarol Rapid 25mg and 50mg tablets except that a larger number of tablets must be taken to achieve the same dose.

CLINICAL PHARMACOLOGY

Bioavailability/bioequivalence

A comparative bioavailability study has been submitted. This was a randomised, single-dose, two-way crossover study comparing a single dose of 12.5mg diclofenac potassium tablet formulations in 66 healthy adult volunteer subjects.

Study design

Sixty-six healthy, adult volunteers were recruited to the bioequivalence study, 44 male and 22 female. The mean height and weight of the subjects was 170cm and 68.7kg respectively. Results from two subjects were excluded from the pharmacokinetic analysis. One subject was withdrawn prior to the second period after testing positive for cocaine. The other subject's results were omitted once it was discovered that they had also been participating in another phase I study.

The test drug material used was Diclofenac potassium 12.5mg tablets manufactured by Pharmaco Ltd, Iceland (now Actavis Ltd). The reference drug material used was Voltarol Dolo 12.5mg tablets manufactured by Novartis, Germany.

A single oral dose of the test or reference product was administered and was repeated after 7 days. Single dosing was performed because the pharmacokinetic characteristics of diclofenac potassium are known. Dosing was repeated after 7 days because the plasma half-life of diclofenac potassium is known and because it was determined that the subjects had no diclofenac potassium in their systems prior to dosing.

Subjects were institutionalised on the evening before each dosing and fasted for 10 hours prior to dosing. Appropriate restrictions on diet, fluid intake and concomitant medications were maintained. Subjects were held for 10 hours after dosing, during which blood samples were taken at intervals appropriate to the known pharmacokinetic profile of diclofenac potassium and were analysed for the drug product concentration.

The following pharmacokinetic parameters were reported: $AUC_{(0-inf)}$, C_{max} , $AUC_{(0-t)}$, T_{max} , $T_{1/2}$ and K_{el} . Analysis of variance was conducted using subject, period, sequence and treatment as variables. 90% confidence intervals (CI) for the ratio of the least squares means of the log-transformed values were presented and compared to the accepted range (80 - 125%).

Overall, the study design was compatible with the Committee for Proprietary Medicinal Products Note for Guidance on the Investigation of Bioavailability and Bioequivalence. It was stated that the study was conducted in compliance with Good Clinical Practice.

Results

There were no protocol deviations which were expected to affect study results.

A summary of the comparative bioavailability results is represented below for log-transformed data:

Parameter (units)	Least squares mean for test product (\pm SD)	Least squares mean for reference (\pm SD)	Ratio (%)	90% CI (non-parametric, %)
$\ln C_{max}$ ($\mu\text{g}/\text{ml}$)	5.6330 \pm 0.51089	5.5776 \pm 0.59990	105.5	93.2-119.5
$\ln AUC_{(0-t)}$ ($\mu\text{g}\cdot\text{h}/\text{ml}$)	5.7035 \pm 0.26774	5.6936 \pm 0.28128	101.1	98.2-104.0
$\ln AUC_{(0-inf)}$ ($\mu\text{g}\cdot\text{h}/\text{ml}$)	5.7098 \pm 0.27003	5.7017 \pm 0.28426	100.9	98.0-103.8

Discussion

These results show that the confidence intervals for all three pharmacokinetic parameters fall within the prescribed limits (80-125%) for bioequivalence.

CLINICAL EFFICACY

No new efficacy data are presented in this application and none are required.

CLINICAL SAFETY

No formal safety data are presented in this application and none are required.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified medic. It is an adequate summary of the clinical data provided in the dossier.

SPC, PIL and LABELS

The SPC, PIL and labels are acceptable.

CONCLUSIONS

Overall, there is no clinical objection to grant a Marketing Authorisation for this application. No new or unexpected safety concerns arose from the application. The SPC, PIL and labelling are satisfactory and are consistent with those for Votarol Rapid 25 and 50mg tablets.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Diclofenac potassium 12.5mg tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Diclofenac potassium 12.5mg tablets and Voltarol Dolo 12.5mg tablets (Novartis, Germany).

No new or unexpected safety concerns arise from these applications.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the reference product are interchangeable. The risk benefit is, therefore, considered to be positive.

**DICLOFENAC POTASSIUM 12.5 MG TABLETS
PL 24668/0001**

STEPS TAKEN FOR ASSESMENT

- 1 The MHRA received the Marketing Authorisation application on 17 August 2005.
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 22 September 2005.
- 3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 22 February 2006 and further information relating to the clinical dossier on 27 July 2006.
- 4 The applicant responded to the MHRA's requests, providing further information on 12 September 2006 relating to the quality and clinical sections.
- 5 The application was determined on 18 December 2006.

**DICLOFENAC POTASSIUM 12.5 MG TABLETS
PL 24668/0001**

STEPS TAKEN AFTER AUTHORISATION – SUMMARY

Date submitted	Application type	Scope	Outcome
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diclofenac potassium 12.5mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet contains and 12.5 mg of Diclofenac potassium..

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated Tablet

White round, unscored biconvex film coated tablet, 5mm diameter, with 'T' marked on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Diclofenac potassium tablets are indicated for:

- Rheumatoid arthritis
- Osteoarthritis
- Low back pain
- Migraine attacks
- Acute musculo-skeletal disorders and trauma such as peri-arthritis (especially frozen shoulder), tendinitis, tenosynovitis, bursitis, sprains, strains and dislocations; relief of pain in fractures
- Ankylosing spondylitis
- Acute gout

- Control of pain and inflammation in orthopaedic, dental and other minor surgery
- Pyrophosphate arthropathy and associated disorders

4.2 Posology and method of administration

It is recommended that the tablets be taken with fluid.

Adults

The recommended daily dose is 100-150mg in two or three divided doses. For milder cases, 75-100 mg daily in two or three divided doses is usually sufficient.

In migraine an initial dose of 50 mg should be taken at the first signs of an impending attack. In cases where relief 2 hours after the first dose is not sufficient, a further dose of 50 mg may be taken. If needed, further doses of 50 mg may be taken at intervals of 4-6 hours, not exceeding a total dose of 200 mg per day.

Children

For children over 14 years of age, the recommended daily dose is 75-100 mg in two or three divided doses. Diclofenac potassium tablets are not recommended for children under 14 years of age.

The use of Diclofenac potassium in migraine attacks has not been established in children.

Elderly

Although the pharmacokinetics of Diclofenac potassium are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs should be used with particular caution in older patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight (also see 'Precautions') and the patient should be monitored for GI bleeding for 4 weeks following initiation of NSAID therapy.

4.3 Contraindications

- Patients with a history of, or active or suspected, gastro-intestinal ulcers or bleeding.
- Previous sensitivity to diclofenac or to any of the excipients in the tablets.
- Patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory agents.
- This product contains soya. If you are allergic to peanut or soya, do not use this medicinal product.

4.4 Special warnings and precautions for use

Warnings

Gastro-intestinal

Close medical surveillance is imperative in patients with symptoms indicative of gastro-intestinal disorders, with a history suggestive of gastro-intestinal ulceration, with ulcerative colitis, Crohn's disease, bleeding diathesis or haematological disorders.

Gastro-intestinal bleeding or ulceration/perforation, haematemesis and melaena have in general more serious consequences in the elderly. They can occur at any time during treatment with or without warning symptoms or a previous history. In the rare instances where gastro-intestinal bleeding or ulceration occurs in patients receiving Diclofenac Potassium the drug should be withdrawn.

Hepatic

Close medical surveillance is imperative in patients suffering from severe impairment of hepatic function.

Hypersensitivity reactions

As with other non-steroidal anti-inflammatory drugs, allergic reactions, including anaphylactic/anaphylactoid reactions, can occur without earlier exposure to the drug.

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

Precautions

Renal, cardiac, hepatic, and elderly

Patients with renal, cardiac or hepatic impairment and the elderly should be kept under surveillance, since the use of NSAIDs may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored.

The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal functions, those being treated with diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of Diclofenac Potassium.

Hepatic

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 Potassium should be discontinued. Hepatitis may occur without prodromal symptoms.

Use of Diclofenac Potassium in patients with hepatic porphyria may trigger an attack.

Haematological

Diclofenac Potassium may reversibly inhibit platelet aggregation (see "Interactions"). Patients with defects of haemostasis should be carefully monitored.

Long term treatment

All patients who are receiving long term treatment with non-steroidal, anti-inflammatory agents should be monitored as a precautionary measure e.g. renal function, hepatic function (elevation of liver enzymes may occur) and blood counts.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of, bronchial asthma.

Caution is required in patients with a history of heart failure or hypertension since oedema has been reported in association with NSAID administration.

4.5 Interaction with other medicinal products and other forms of interaction

Lithium and digoxin

Diclofenac Potassium may increase plasma concentrations of lithium and digoxin.

Anticoagulants

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

Antidiabetic agents

Clinical studies have shown that Diclofenac Potassium can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic effects which have required adjustment to the dosage of hypoglycaemic agents.

Ciclosporin

Cases of nephrotoxicity have been reported in patients receiving concomitant ciclosporin and NSAIDs, including Diclofenac Potassium. This might be mediated through combined renal anti-prostaglandin effects of both the NSAID and ciclosporin.

Methotrexate

Cases of serious toxicity have been reported when methotrexate and NSAIDs 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.

Quinolone Antibacterials

Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients already receiving an NSAID.

Other NSAIDs and corticosteroids

Co-administration of Diclofenac Potassium with aspirin or corticosteroids may increase the risk of gastro-intestinal bleeding. Avoid concomitant use of two or more NSAIDs.

Diuretics

Like other NSAIDs, Diclofenac Potassium may inhibit the activity of diuretics. Concomitant treatment with potassium sparing diuretics may be associated with increased serum potassium levels, which should therefore be monitored frequently.

Cardiac glycosides

Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Mifepristone

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

Anti-hypertensives

Concomitant use of NSAIDs with antihypertensive drugs (i.e. beta-blockers, angiotensin converting enzyme (ACE) inhibitors, diuretics) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

4.6 Pregnancy and lactation

Although animal studies have not demonstrated teratogenic effects, Diclofenac Potassium should not be prescribed during pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used.

Congenital abnormalities have been reported in association with the administration of NSAIDs in man; however, these are low in frequency and do not appear to follow any discernible pattern.

In view of the known effects of NSAIDs on the foetal cardiovascular system (e.g. a premature closure of the ductus arteriosus) and in causing uterine inertia, use in late pregnancy should be avoided.

Following oral doses of 50 mg every 8 hours, traces of active substance have been detected in breast milk, but in quantities so small that no adverse effects on the breast-fed infant are to be expected.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness or other central nervous disturbances while taking NSAIDs should refrain from driving or operating machinery.

4.8 Undesirable effects

If serious side-effects occur, Diclofenac Potassium should be withdrawn.

Frequency estimate:

frequent:>10 %

occasional:>1 - 10 %

rare:>0.001 - 1 %

isolated cases: <0.001 %.

Gastro-intestinal tract:

Occasional: Epigastric pain, other gastro-intestinal disorders (e.g. nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia).

Rare: Gastro-intestinal bleeding (haematemesis, melaena, bloody diarrhoea), gastro-intestinal ulcers with or without bleeding or perforation.

In isolated cases: Aphthous stomatitis, glossitis, oesophageal lesions, lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbations of ulcerative colitis or Crohn's proctocolitis, colonic damage and stricture formation), pancreatitis, constipation.

Central nervous system:

Occasional: Headache, dizziness, vertigo.

Rare: Drowsiness, tiredness.

In isolated cases: Disturbances of sensation, paraesthesia, memory disturbance, disorientation, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions, aseptic meningitis.

Special senses:

Isolated cases: Disturbances of vision (blurred vision, diplopia), impaired hearing, tinnitus, taste disturbances.

Skin:

Occasional: Rashes or skin eruptions.

Rare: Urticaria

In isolated cases: Bullous eruptions, eczema, erythema multiforme, Stevens- Johnson syndrome, Lyell's syndrome, (acute toxic epidermolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, purpura including allergic purpura.

Kidney:

Rare: Oedema

In isolated cases: Acute renal insufficiency, urinary abnormalities (e.g. haematuria, proteinuria), interstitial nephritis, nephrotic syndrome, papillary necrosis.

Liver:

Occasional: Elevation of serum amino-transferase enzymes (ALT, AST).

Rare: Liver function disorders including hepatitis with or without jaundice.

In isolated cases: Fulminant hepatitis.

Blood:

In isolated cases: Thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia.

Hypersensitivity:

Rare: Hypersensitivity reactions (e.g. bronchospasm, anaphylactic/ anaphylactoid systemic reactions including hypotension).

Isolated cases: Vasculitis, pneumonitis.

Cardiovascular system:

Isolated cases: Palpitations, chest pain, hypertension, congestive heart failure.

Other organ systems:

Isolated cases: Impotence.

4.9 Overdose

Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures. There is no typical clinical picture resulting from Diclofenac Potassium overdosage.

The therapeutic measures to be taken are: absorption should be prevented as soon as possible after overdosage by means of gastric lavage and treatment with activated charcoal; supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation, and respiratory depression; specific therapies such as forced diuresis, dialysis or haemoperfusion are unlikely to be helpful in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: NSAID, ATC code: {M01 AB 05}

Diclofenac potassium tablets contain the potassium salt of diclofenac, a non-steroidal compound with pronounced and clinically demonstrable analgesic, anti-inflammatory and anti-pyretic properties.

Diclofenac is a potent inhibitor of prostaglandin bio-synthesis and modulator of arachidonic acid release and uptake.

Diclofenac potassium tablets have a rapid onset of action and are, therefore, suitable for the treatment of acute episodes of pain and inflammation.

In migraine attacks Diclofenac potassium has been shown to be effective in relieving the headache and in improving the accompanying symptom of nausea.

Diclofenac *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

5.2 Pharmacokinetic properties

Absorption

Diclofenac is rapidly and completely absorbed from sugar-coated tablets. Food intake does not affect absorption.

Peak plasma concentration after one 12.5 mg tablet was 0.944 µmol/l after 54 minutes. The plasma concentrations show a linear relationship to the size of the dose.

Diclofenac undergoes first-pass metabolism and is extensively metabolised.

Distribution

Diclofenac is highly bound to plasma proteins (99.7%), chiefly albumin (99.4%)

Elimination

The total systemic clearance of diclofenac in plasma is 263 ± 56 ml/min (mean \pm SD).

The terminal half-life in plasma is 1-2 hours.

Repeated oral administration of Diclofenac Potassium for 8 days in daily doses of 50 mg t i d does not lead to accumulation of diclofenac in the plasma.

Approx. 60% of the dose administered is excreted in the urine in the form of metabolites, and less than 1% as unchanged substance. The remainder of the dose is eliminated as metabolites through the bile in the faeces.

Biotransformation

The biotransformation of diclofenac involves partly glucuronidation of the intact molecule but mainly single and multiple hydroxylation followed by glucuronidation.

Characteristics in patients

The age of the patient has no influence on the absorption, metabolism, or excretion of diclofenac.

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 theoretical steady-state plasma levels of metabolites are about four times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

In the presence of impaired hepatic function (chronic hepatitis, non-decompensated cirrhosis) the kinetics and metabolism are the same as for patients without liver disease.

5.3 Preclinical safety data

Relevant information on the safety of Diclofenac potassium is included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Silica colloidal anhydrous
Sodium starch glycollate
Povidone
Starch maize
Calcium hydrogen phosphate anhydrous
Magnesium stearate

Film coating:

Polyvinyl alcohol partially hydrolysed
Titanium dioxide E171
Talc
Lecithin soya E322
Xanthan gum E415

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25 °C

6.5 Nature and contents of container

Blister pack. Pack sizes: 7, 10, 14, 28, 30, 50, 56, 98 and 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited

6th Floor

94 Wigmore Street

London

W1U 3RF

UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 24668/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/12/2006

10 DATE OF REVISION OF THE TEXT

18/12/2006

PATIENT INFORMATION LEAFLET



DICLOFENAC POTASSIUM 12.5mg TABLETS PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Diclofenac potassium 12.5mg Tablets are and what they are used for
2. Before you take Diclofenac potassium 12.5mg Tablets
3. How to take Diclofenac potassium 12.5mg Tablets
4. Possible side effects
5. Storing Diclofenac potassium 12.5mg Tablets

The name of this medicine is Diclofenac potassium 12.5mg Tablets

- The active substance is Diclofenac. Each tablet contains 12.5mg Diclofenac potassium.
- The tablets also contain silica colloidal anhydrous, sodium starch glycolate, povidone, maize starch, calcium hydrogen phosphate anhydrous, magnesium stearate, polyvinyl alcohol partially hydrolysed, Titanium dioxide E171, talc, lecithin soya E322 and Xanthan gum E415.
- They are supplied in blister packs of *7, 10, 14, 28, 30, 50, 56, 98 and 100 film coated tablets.
- This medicine contains 0.0374 mmol (1.46mg) potassium per tablet. To be taken into account by patients with reduced kidney function or patients on a controlled potassium diet.

**(Final printed leaflet to include only marketed pack sizes).*

Diclofenac potassium is one of a group of medicines called non-steroidal anti-inflammatory analgesics (NSAIDs). NSAIDs reduce pain and inflammation.

Product Licence Holder: Caduceus Limited, 6th Floor, 94 Wigmore Street, London, W1U 3RF, UK

Manufactured By: Actavis hf., Reykjavikurvegi 78, PO Box 420, IS-222, Hafnarfjörður, Iceland.

Product Licence Number: PL 24668/0001

1. WHAT DICLOFENAC POTASSIUM 12.5mg TABLETS ARE AND WHAT THEY ARE USED FOR

Diclofenac potassium relieves the symptoms of inflammation and pain.

The tablets are used for the treatment of:

- Sprains, strains and other injuries
- Pain and swelling following surgery
- Gout
- Other painful conditions affecting the joints and muscles such as backache.

They can also be used to relieve the symptoms associated with migraine attacks in adults. Doctors sometimes prescribe Diclofenac potassium for other purposes; ask your doctor for information.

2. BEFORE YOU TAKE DICLOFENAC POTASSIUM 12.5mg TABLETS

Do not take Diclofenac potassium 12.5mg Tablets and tell your doctor if:

- Are allergic to diclofenac or any of the inactive ingredients (refer to the list above)
- You have or have you ever had an ulcer in the gullet, stomach or upper bowel or gastro-intestinal bleeding, symptoms of which may include blood in vomit, bleeding when emptying bowels (or fresh blood in stools) or black, tarry stools
- Have had any breathing problems, a runny nose or skin rash after taking aspirin or any other NSAID?

It is important to tell your doctor before taking this medicine about other conditions you may have. Your doctor may need to monitor you more closely. Tell your doctor if:

- you suffer from any bowel disorders, for example, ulcerative colitis or Crohn's disease?
- you suffer from heart, kidney, or liver problems?

- you suffer from any blood or bleeding disorder? If you do, your doctor may ask you to go for regular check-ups whilst you are taking these tablets.
- you have, or have you ever had bronchial asthma?
- you have, or have you ever had a heart condition or high blood pressure?

Whilst you are taking these tablets, your doctor may want to give you a check-up from time to time. This medicine may make you feel dizzy or drowsy when you start to take it. Do not drive or work machinery until these effects wear off. Diclofenac potassium Tablets are not recommended for children under the age of 14.

Pregnancy

Are you pregnant, planning to become pregnant? Although not common, abnormalities have been reported in babies whose mothers have taken NSAIDs during pregnancy. You should not use Diclofenac potassium Tablets during the late phase of pregnancy as it may affect the baby's blood circulation.

Breast-feeding

Ask your doctor or pharmacist before taking any medicine.

Important information about some of the ingredients in Diclofenac Potassium 12.5 mg Tablets

This product contains soya. If you are allergic to peanut or soya, do not use this medicinal product.

Taking Diclofenac potassium Tablets with other medicines

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines even if not prescribed. Some medicines can interfere with Diclofenac so consult your doctor or pharmacist before taking any other medication. In particular, tell your doctor if you are taking any of the following medicines

- Medicines to treat diabetes
- Anticoagulants (blood thinning tablets like warfarin)
- Diuretics (water tablets)
- Lithium
- Digoxin
- Methotrexate
- Ciclosporin
- Antibiotics
- Steroids
- Any other NSAID e.g. aspirin or ibuprofen
- Medicines to treat heart conditions including high blood pressure
- Mifepristone (a medicine used during termination of pregnancy)?

If you go into hospital or to the dentist for treatment, make sure the doctor or dentist knows you are taking Diclofenac potassium Tablets.

3. HOW TO TAKE DICLOFENAC POTASSIUM 12.5mg TABLETS

Follow your doctor's instructions. Check the label to see how often you should take your tablets. In adults the usual dose of Diclofenac potassium to treat pain and swelling is 100 mg to 150 mg each day, divided into two or three doses. In milder cases 75 mg to 100 mg daily divided into two or three doses is usually sufficient. Lower doses may be used in elderly patients. If you are frail or you are elderly and have a low body weight, your doctor may ask you to go back to see him regularly for the first 4 weeks of treatment, to make sure that you are not getting any side effects.

For the treatment of the symptoms of migraine in adults, 4 tablets, are usually taken when the first signs of a migraine attack appear. Another 4 tablets can be taken 2 hours after the first if needed and then at 4 to 6 hourly intervals. You should never take more than 16 tablets (200 mg) in 24 hours. These tablets are not suitable for the treatment of migraine in children.

In children over 14 years of age the usual dose is 75 mg to 100 mg (6-8 tablets) daily, divided into two or three doses.

If you are not sure about the dose, check with your doctor or pharmacist.

Do not take more than your doctor has recommended.

Take your tablet whole with a glass of water, preferably before meals.

If you forget to take a tablet, take another as soon as you remember or wait until the next dose is due then continue as before. Do not take a double dose to make up for forgotten individual doses. Do not take more than 16 tablets in 24 hours.

If you take more Diclofenac potassium Tablets than you should:

Contact your doctor immediately or go to your nearest Accident and Emergency department. Take along this leaflet, the carton and any remaining tablets, so that the medical staff know exactly what you have taken.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Diclofenac potassium 12.5mg Tablets can have undesirable effects in some people.

STOP taking the tablets and tell your doctor if you get any of the following:

- Stomach pain, indigestion, heartburn, wind, nausea or vomiting
- Any sign of bleeding in the stomach or intestine, e.g. bleeding when emptying your bowels (or fresh blood in the stools), blood in vomit or black, tarry stools
- Skin rash, itching or bruising or painful red areas
- Wheezing or shortness of breath
- Yellowing of your skin or the whites of your eyes
- Persistent sore throat or high temperature
- An unexpected change in the amount of urine produced and/or its appearance.

If you notice that you are bruising more easily than usual or have frequent sore throats or infections, tell your doctor.

People who have used Diclofenac potassium have reported side-effects to varying degrees:

Occasional side-effects, reported in 1 in 100 to 1 in 10 people include:

Effects on the nervous system: Headache, dizziness, vertigo

Effects on the stomach and digestive system: Feeling or being sick, diarrhoea, stomach pain, wind, loss of weight or poor appetite, heartburn,

Effects on the liver: abnormal liver function tests,

Effects on the skin: Skin rashes

Rare side-effects, reported in 1 in 100 000 to 1 in 100 people include:

Effects on the nervous system: Drowsiness, tiredness

Effects on the stomach and digestive system: Stomach ulcers or bleeding

Effects on the chest: Bronchospasm (symptoms of which include difficulty in breathing)

Effects on the heart: Hypotension (low blood pressure, symptoms of which may include faintness, giddiness or light headedness)

Effects on the liver: hepatitis and jaundice

Effects on the skin: itching

Other effects: Fluid retention, symptoms of which include swollen ankles

Isolated side-effects, reported in less than 1 in 100 000 people include:

Effects on the nervous system: Tingling or numbness in the fingers, tremor, blurred or double vision, hearing loss or impairment, tinnitus (ringing in the ears), difficulty sleeping, nightmares, mood changes, disorientation and loss of memory, fits, headaches together with a dislike of bright lights and a stiff neck, disturbances in sensation, taste disturbance.

Effects on the stomach and digestive system: Constipation inflammation of the tongue, mouth ulcers and ulcers of the gullet, lower gut disorders (including inflammation of the colon causing diarrhoea and stomach pains).

Effects on the heart, chest or blood: palpitations (fast or irregular heart beat), chest pain, hypertension (high blood pressure), inflammation of blood vessels (vasculitis), inflammation of the lung (pneumonitis), congestive heart failure, blood disorders (including anaemia, making you tired and more prone to minor infections or bleeding)

Effects on the liver or kidneys: Kidney or liver disorders which may make you tired and cause yellowing of the skin, presence of blood or protein in the urine

Effects on skin or hair: Skin rashes which may be made worse by exposure to sunlight, hair loss

Other effects: Inflammation of the pancreas, impotence (difficulty getting an erection)

Do not be alarmed by this list - most people take Diclofenac potassium without any problems.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING DICLOFENAC POTASSIUM 12.5mg TABLETS

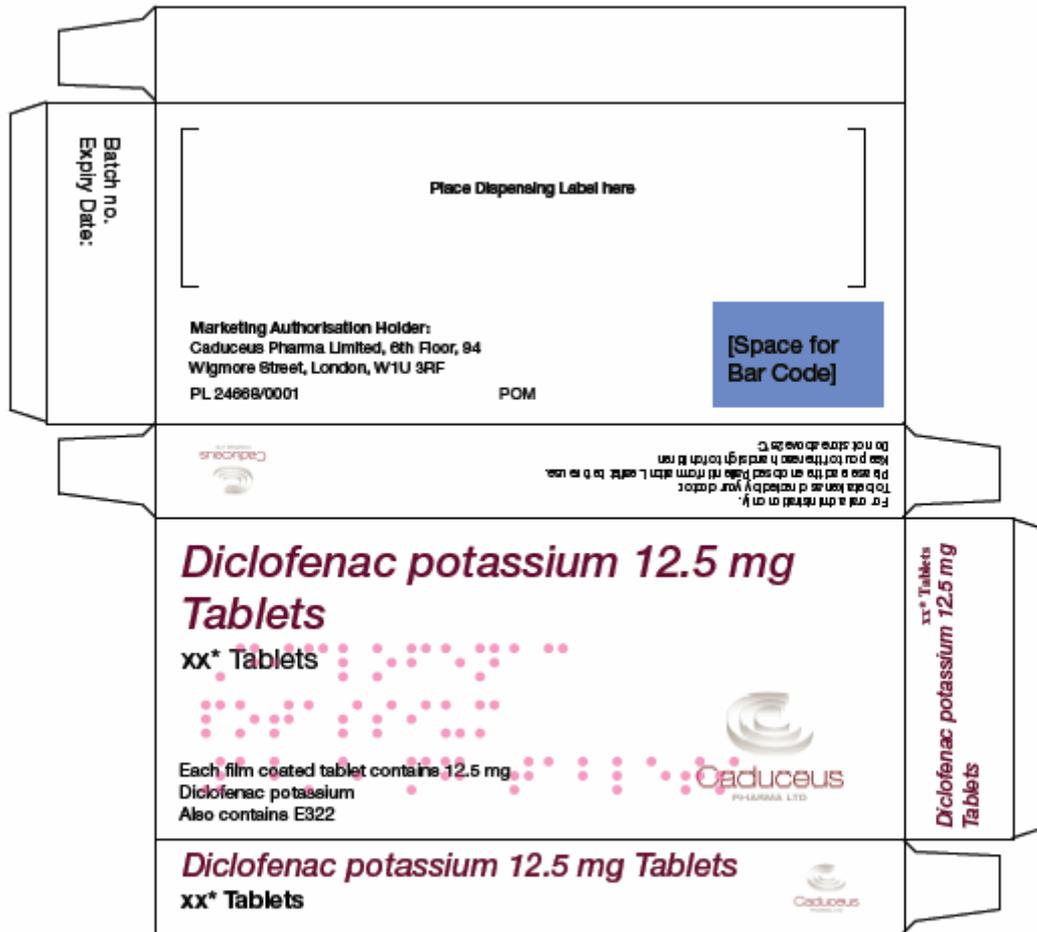
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

Do not store above 25 °C

Do not use after the expiry date stated on the carton. Unused tablets should be taken back to the pharmacist for safe disposal.

This leaflet was last revised in August 2006

LABELLING



(All dimensions are approximate)

* 7, 10, 14, 28, 30, 50, 56, 98 or 100 Tablets. Only the marketed pack sizes will be stated on the actual printed cartons

The Batch Number and Expiry Date will be embossed on to the actual cartons.

Diclofenac potassium 12.5mg Tablets
PL 24668/0001
Blister Foil Mock-up



Exact dimensions to be confirmed.

*The Batch Number and Expiry Date will be embossed on to the actual blister pack.