

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1380/078/001

Case No: 1999941

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Actavis Group PTC ehf

Reykjavikurvegi 76-78, 220 Hafnarfjordur, Iceland

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Kyflam 25mg Film-coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **28/08/2009** until **27/08/2014**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Kyflam 25 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg of diclofenac potassium.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

Pink, circular, coated, biconvex.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short-term treatment of all grades of pain and inflammation in the following acute conditions:

- Post traumatic pain, inflammation and swelling, e.g. due to sprains.
 - Acute musculo-skeletal disorders such as periarthrits (for example frozen shoulder), tendonitis, tenosynovitis, bursitis.
 - 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 and associated menorrhagia.
 - Migraine attacks.
 - Acute gout.
 - Painful syndromes of the vertebral column.
 - Non-articular rheumatism.
 - As an adjuvant in severe painful inflammatory infections of the ear, nose or throat, e.g. pharyngotonsillitis, otitis.
- In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Fever alone is not an indication.

4.2 Posology and method of administration

For oral administration.

To be taken preferably with or after food.

The tablets should be swallowed whole with liquid

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

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. The recommended maximum daily dose of diclofenac is 150 mg.

In migraine an initial dose of 50 mg should be taken at the first signs of an impending attack. In cases where pain relief within 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: The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID 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.

4.3 Contraindications

- Hypersensitivity to diclofenac potassium or to any of the excipients.
- Active, or history of recurrent peptic ulcer / haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- 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)
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- 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

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 Kyflam 25mg Film-coated Tablets with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

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

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).

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.

Respiratory disorders:

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.

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.

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, the elderly or those recovering from major surgery.

Renal Function should be monitored in these patients (see also section 4.3). Effects on renal function are usually reversible on withdrawal of diclofenac potassium.

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

Use of diclofenac potassium in patients with hepatic porphyria may trigger an attack.

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.

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 suggest that use of diclofenac, particularly at high dose (150mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac potassium after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Gastrointestinal bleeding, ulceration and perforation:

GI bleeding, 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 GI events.

The risk of GI 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 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 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI 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, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving diclofenac potassium, 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).

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).

Dermatological:

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 the 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. Kyflam 25mg Film-coated Tablets should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

Hypersensitivity reactions:

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

Impaired female fertility:

The use of Kyflam tablets 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 Kyflam tablets should be considered.

Haematological:

As with other NSAIDs, diclofenac potassium may reversibly inhibit platelet aggregation (see anticaagulants in “Drug interactions”). Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

Long term treatment:

All patients who are receiving non-steroidal, anti-inflammatory agents should be monitored as a precautionary measure eg renal function, hepatic function (elevation of liver enzymes may occur) and blood counts. This is particularly important in the elderly.

4.5 Interaction with other medicinal products and other forms of interaction

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).

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 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 and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4 Special warnings and precautions for use).

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

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

Digoxin: Diclofenac potassium may increase plasma concentrations of digoxin.

Methotrexate: Decreased elimination of 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.

Ciclosporin: Increased risk of nephrotoxicity.

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.

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

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

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (See section 4.4).

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.

Anti-platelet agents: increased risk of gastrointestinal bleeding (see section 4.4).

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.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

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.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4 Special warnings and precautions for use).

4.6 Pregnancy and lactation

Pregnancy:

Congenital abnormalities have been reported in association with NSAID administration 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 (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3). NSAIDs 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.

Lactation:

In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

Fertility

As with other NSAIDs, the use of diclofenac potassium 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 potassium should be considered.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), including isolated reports. Frequency estimate: frequent $> 10\%$, occasional $> 1\% - 10\%$, rare $> 0.001\% - 1\%$, isolated cases $< 0.001\%$.

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4 Special warnings and precautions for use). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of coillitis and Crohn's disease (see section 4.4 Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

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

Blood and lymphatic system disorders

Very rare: Thrombocytopenia, leucopenia, anaemia (including haemolytic anaemia 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, nightmares, irritability, psychotic disorders.

Nervous system disorders

Common: Headache, dizziness.

Rare: Somnolence.

Very rare: Paraesthesias, memory impairment, convulsions, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.

Eye disorders

Very rare: Visual disturbance, vision blurred, diplopia.

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, 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, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation).

Very rare: Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.

Hepatobiliary disorders

Common:	Transaminases increased.
Rare:	Hepatitis, jaundice, liver disorder.
Very rare:	Fulminant hepatitis.

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, pruritis.

Renal and urinary disorders

Very rare:	Acute renal failure haematuria, proteinuria, nephritic syndrome, interstitial nephritis, renal papillary necrosis.
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General disorders and administration site conditions

Rare:	Oedema.
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Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that the use of diclofenac, particularly at high doses (150 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4 Special warnings and precautions for use).

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 are possible.

Therapeutic measures

Management of acute poisoning with NSAIDs consists essentially 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 unlikely to be helpful in accelerating the eliminating NSAIDs due to the 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.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances (NSAID) (ATC code: M01A B05).

Mode of action: Diclofenac potassium is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase (cyclo-oxygenase). Diclofenac potassium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings. Kyflam tablets have a rapid onset of action which makes them particularly suitable for the treatment of acute painful and inflammatory conditions.

In migraine attacks, diclofenac potassium has been shown to be effective in relieving the headache and in improving the accompanying nausea and vomiting symptoms.

5.2 Pharmacokinetic properties

Absorption: Diclofenac is rapidly and completely absorbed from Kyflam tablets. The absorption sets in immediately after administration and the same amount is absorbed as from an equivalent dose of diclofenac sodium gastro-resistant tablets. Mean peak plasma concentrations of 3.8 µmol/L are attained after 20-60 minutes after ingestion of one tablet of 50mg. Ingestion together with food has no influence on the amount of diclofenac absorbed although onset and rate of absorption may slightly delayed.

The amount absorbed is in linear proportion to the size of the dose.

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

Distribution: The active substance is 99.7% protein bound, mainly to albumin (99.4%).

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

Metabolism: Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination: Total systemic clearance of diclofenac in plasma is 263 ± 56 ml/min (mean value $\pm$ SD). The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours.

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.

Patients with renal impairment: 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 <10mL/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.

Patients with hepatic disease: 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

Diclofenac did not influence fertility of the parent animals (rats) nor the pre-, peri-, and postnatal development of the offspring. No teratogenic effects were detected in mice, rats and rabbits. No mutagenic effects could be demonstrated in various in vitro and in vivo experiments, and no carcinogenic potential was detected in long-term studies in rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica colloidal anhydrous
Sodium starch glycolate Type A
Povidone
Starch maize
Calcium hydrogen phosphate anhydrous
Magnesium stearate

Film Coating:
Polyvinyl alcohol partially hydrolysed
Titanium dioxide (E171)
Talc
Lecithin soya (E322)
Iron oxide red (E172)
Xanthan gum (E145)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Blister: Store in the original package
Container: Keep the container tightly closed

6.5 Nature and contents of container

Al/Al Blister or PP Tablet Container with LDPE Cap with desiccant

Pack sizes: 7, 14, 21, 28, 30, 50, 56, 60, 84, 100 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/078/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th August 2009

10 DATE OF REVISION OF THE TEXT