SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Akis 50 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is diclofenac sodium

Each 1 ml ampoule contains:

50 mg of diclofenac sodium

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection

Clear to slightly amber coloured transparent solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Akis Solution for Injection is effective in acute forms of pain, including renal colic, exacerbations of osteo- and rheumatoid arthritis, acute back pain, acute gout, acute trauma and fractures, and post-operative pain (see section 4.3 and 4.4).

Akis is indicated in adults. Use in children and adolescents is not recommended.

4.2 Posology and method of administration

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

Posology

Adults

AKIS Solution for Injection can be administered intramuscularly or subcutaneously. AKIS is for short-term treatment only and should not be given for more than two days.

For mild and moderate grades of pain a lower dose may be sufficient. A dose of 75 mg may be needed for severe pain such as renal colic. Exceptionally and in severe cases a second dose of 75 mg can be administered after 6 hours. A dose of 150 mg must not be exceeded within any 24 hour period.

If more than one daily injection of AKIS is required, (up to a maximum, daily dose of 150 mg) it is advisable to change the injection area for subsequent injections. If necessary, one injection of AKIS can be used with other dosage forms of diclofenac up to the maximum daily dosage of 150mg.

Special populations

Elderly
The elderly are at increased risk of serious adverse reactions (see section 4.4 and 5.2). 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. The recommended maximum daily dose of AKIS Solution for Injection is 150 mg.

Patients with renal impairment
Hydroxypropyl-β-cyclodextrin (HPβCD), an excipient in AKIS Solution for Injection, is mainly eliminated through glomerular filtration. Therefore, patients with severe renal impairment (defined as creatinine clearance below 30 ml/min) should not be treated with AKIS Solution for Injection. (See section 4.4 and 5.2). In patients with renal impairment the lowest effective dose should be used.

Paediatric population
The safety and efficacy of AKIS Solution for Injection in children aged 0-18 years has not been established.

Method of administration

AKIS Solution for Injection should only be administered by a healthcare professional. It can be administered intramuscularly or subcutaneously into clean healthy tissue.

A single vial must be used rather than two vials to make up a known dose e.g. a single 75 mg injection rather than a 25mg and a 50 mg injection or a 50mg injection rather than two 25 mg injections.

Intramuscularly
The following directions for intramuscular injection must be adhered to in order to avoid damage to a nerve or other tissue at the injection site. A deep intragluteal injection into the upper outer quadrant of the buttock must be administered. If two injections daily are required, it is advised that the alternative buttock be used for the

second injection. The product should be injected slowly to minimise local tissue damage.

Subcutaneously
The injection must be administered into the subcutaneous tissue, preferably in the upper part of the gluteus or in the upper part of the thigh. If two injections daily are required, it is advisable to rotate the injection area between the gluteus and the thigh. The needle must be fully introduced into the thickness of the skin fold which forms between the thumb and the index finger. Care should be taken to ensure that a blood vessel has not been entered. The product should be injected slowly and at a steady rate. Keep the skin folded between the fingers during injection.

AKIS must not be given by intravenous (i.v.) administration.

Please refer to section 6.6 for instructions for use and handling.

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation
- History of gastrointestinal bleeding or perforation related to previous NSAID therapy.
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Last trimester of pregnancy (see section 4.6)
- Severe hepatic renal or cardiac failure (see section 4.4).
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Diclofenac is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.
- Haemostasis disorders or current anticoagulant treatment (for intramuscular route of administration only).
- 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

General
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 concomitant use of Diclofenac with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.

Caution is indicated in the elderly on the basis of 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.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug.
Like other NSAIDs, Diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties.

The instructions for intramuscular injection should be strictly followed in order to avoid adverse events at the injection site, which may result in muscle weakness, muscle paralysis, hypoaesthesia and injection site necrosis.

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

As with all NSAIDs, including Diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Diclofenac in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.8). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

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

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

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors (see section 4.5). Close medical surveillance and caution should be exercised in patients with ulcerative colitis or Crohn’s disease, as their condition may be exacerbated (see section 4.8).

Hepatic effects
Close medical surveillance is required when prescribing Diclofenac to patients with impaired hepatic function, as their condition may be exacerbated. As with other NSAIDs including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with Diclofenac, regular monitoring of hepatic function is

indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), Diclofenac should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.
Caution is called for when using Diclofenac in patients with hepatic porphyria, since it may trigger an attack.

Renal effects

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

The excipient HPβCD is predominantly eliminated through the kidney by glomerular filtration. Therefore, patients with severe renal impairment (defined as creatinine clearance below 30 ml/min) should not be treated with AKIS injectable solution. In patients with renal impairment, the lowest effective dose should be used.

Skin effects
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 higher 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. AKIS should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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 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).
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.

Haematological effects
During prolonged treatment with Diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Like other NSAIDs, Diclofenac may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

Anaemia may occur as a result of water retention or effects on erythropoiesis.

Consequently it is advisable to monitor the levels of haemoglobin and haematocrit if symptoms of anaemia are detected. Hyperpotassemia may occur in diabetic patients or those who are also taking potassium-sparing drugs (see section 4.5).

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.

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 section 4.8).
Administration
Injections must be carried out following strict rules of asepsis and antisepsis.

Duration of treatment
Akis must not be administered for longer than 2 days. After 2 days, the need for an alternative NSAID should be reviewed and if long-term treatment with an NSAID is required, patients should be monitored for evidence of renal and hepatic dysfunction and blood count abnormalities. This is particularly important in the elderly.

4.5 Interactions with other medicinal products and other forms of interaction

The following interactions include those observed with Diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.

Lithium: NSAIDs have been reported to increase blood lithium levels via decreased renal excretion of lithium. If this combination is considered necessary, lithium plasma concentrations should be monitored carefully during the initiation, adjustment and withdrawal of diclofenac treatment.

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

Diuretics, ACE inhibitors and Angiotensin-II Antagonists: NSAIDs may reduce the antihypertensive effect of diuretics and other antihypertensive drugs (such as beta-blockers, angiotensin converting enzyme (ACE) inhibitors). In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin-II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter (see also section 4.4).

Other NSAIDs, corticosteroids and acetylsalicylic acid: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids or acetylsalicylic acid may increase the frequency of gastrointestinal undesirable effects (see section 4.4) and is not recommended.

Anticoagulants and heparin (administered in the elderly or at curative doses): Caution is recommended since concomitant administration with NSAIDs could increase the risk of bleeding via inhibition of platelet function and damage to the gastroduodenal mucosa (see section 4.4). NSAIDs may enhance the effects of anti-coagulants such as warfarin and heparin. Heparin is not recommended for administration to elderly patients or at curative doses. Careful monitoring of the international normalized ratio (INR) is required if co-administration cannot be avoided. Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Thrombolytics and anti-platelet agents: Caution is recommended since concomitant administration with NSAIDs could cause increased risk of bleeding via inhibition of platelet function and damage to the gastroduodenal mucosa.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4).

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic 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.

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 or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased. Weekly blood count monitoring during the first

few weeks of the combination is recommended. Monitoring should be increased in patients with impaired kidney function or in elderly subjects.

Pemetrexed in patients with normal renal function, CLcr > 80 ml/min: Increased risk of pemetrexed toxicity due to decrease in pemetrexed clearance. Biological monitoring of renal function is recommended.

Calcineurin inhibitors (e.g. Ciclosporin, tacrolimus): Nephrotoxicity of calcineurin inhibitors may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment, monitoring of renal function is recommended, especially in the elderly

Deferasirox: The concomitant administration of NSAIDs and deferasirox may increase the risk of gastrointestinal toxicity. Close clinical monitoring should be performed when these drugs are combined.

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

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

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 sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentration and exposure to diclofenac due to inhibition of diclofenac metabolism.

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

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.

Despite being extensively bound to proteins, AKIS does not interfere with the protein binding of: salicylates, tolbutamide, and prednisolone.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 of 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 been 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 the organogenetic period. During the first and second trimester of pregnancy, diclofenac should not be given unless clearly necessary. If diclofenac is used by a woman attempting to conceive, or during the first and second 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 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

Lactation

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

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 have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac should be considered.

4.7 Effects on ability to drive and use machines

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking Diclofenac, should refrain from driving or using machines.

4.8 Undesirable effects

Clinical trials

The most common undesirable effects observed during clinical trials with AKIS are gastrointestinal in nature or injection site reactions which are generally mild and transitory.

Clinical trial data suggest that the use of diclofenac injectable solution is associated with injection site reactions, such as: pain and haematoma. The frequency of injection site adverse events was significantly lower at the 25 and 50 mg dose than at the 75 mg dose. After administering diclofenac the following have also been reported: nausea, vomiting, diarrhoea and constipation.

The undesirable effects are presented below according to MedDRA System Organ Class classification (SOC) and frequency of observation, in accordance with the following convention: very common (≥1/10); common (≥1/100 - <1/10); uncommon (≥1/1000 - <1/100); rare (≥1/10000 - <1/1000); very rare (<1/10000), not known (cannot be estimated from the data available).

Body system	**Frequency**	**Adverse Drug Reaction**
Infection and infestations	Not known	Injection site necrosis
Nervous system disorders	Uncommon	Dizziness Headache
Gastrointestinal disorders	Common Uncommon Not known	Nausea Diarrhoea Vomiting Constipation Gastritis Ischaemic colitis
Hepatobiliary disorders	Uncommon	Hepatic enzymes increase
Skin and subcutaneous tissue disorders	Uncommon	Pruritus
General disorders and administration site conditions	Very common	Injection site reactions

The most appropriate MedDRA term is listed to describe a certain reaction. Synonyms or related conditions are not listed, but should be taken into consideration as well.

Class effects

Adverse reactions (Table 1) are ranked under 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, <1/1,000); very rare (<1/10,000); Not known: cannot be estimated from the available data.

The following undesirable effects include those reported with either short-term or long-term use.

Table 1

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), Agranulocytosis.
Immune system disorders	
Rare Very rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock). Angioneurotic oedema (including face oedema).
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common Rare Very rare	Headache, dizziness. Somnolence. Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.
Eye disorders	
Very rare	Visual disturbance, vision blurred, diplopia.
Ear and labyrinth disorders	
Common Very rare	Vertigo. 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 Very rare	Asthma (including dyspnoea). Pneumonitis.
Gastrointestinal disorders	
Common Rare Very rare	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia. Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation). 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 Rare Very rare	Transaminases increased. Hepatitis, jaundice, liver disorder. Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common Rare Very rare	Rash. Urticaria. 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	
Common Rare	Injection site reaction, injection site pain, injection site induration Oedema Injection site necrosis.
Infections and infestations	
Very rare	Injection site abscess.

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 internet at www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac over dosage. Over dosage 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, including diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: non-steroidal antinflammatory drugs (NSAIDs):

ATC Code: M01AB05.

It is therapeutic subgroup classification: musculo-skeletal system/anti-inflammatory and antirheumatic products/ non-steroids/acetic acid derivatives and related substances

Mechanism of action:

Akis Solution for Injection is a nonsteroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase). Diclofenac sodium *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings. When used concomitantly with opioids for the management of post-operative pain, diclofenac sodium often reduces the need for opioids.

Clinical efficacy:

The analgesic efficacy of Akis 25, 50 and 75 mg solution for injection was evaluated in two pivotal dental pain studies. Patients with moderate to severe pain following dental impaction surgery were included in these studies.

In one study the analgesic efficacy of Akis 25, 50 and 75 mg/ml subcutaneously administered was compared to placebo. Akis at all strengths produced a statistically significant higher pain relief (as measured on the VAS) compared to placebo ($p<0.001$). Akis also produced significantly higher analgesia compared to placebo in the secondary efficacy measures, time to onset of analgesia, use of rescue medication over the 8 hours following drug administration and patients with a 30% reduction in pain intensity at 1.5 hours following drug administration ($p<0.001$ in all comparisons to placebo; no statistical difference was detected in the comparisons between the active drugs).

In the second dental pain study the analgesic efficacy of Akis 75 mg/ml subcutaneosly administered was compared to that of Voltarol® 75 mg/3 ml intramuscularly administered. No significant difference between the two treatments was observed at any time point over the 8 hours following drug administration. At 1.5 hours following drug administration (primary endpoint of the study), the 95% CI of the difference between the two treatments was entirely above the pre-defined margin of non-inferiority (-15 mm). Akis was therefore proved to be therapeutically equivalent to Voltarol. The mean differences and 95% CIs of the difference at any time point over the 8 hours following drug administration are shown in the table below.

Assessment time point	Means difference (95% CI)	p-value
15 minutes	0.7 (-4.02 ; 5.41)	0.7708
30 minutes	1.6 (-4.26 ; 7.55)	0.5826
45 minutes	1.3 (-4.93 ; 7.48)	0.6857
1 hour	-2.1 (-8.63 ; 4.44)	0.5272
1.5 hours	-1.8 (-8.26 ; 4.61)	0.5764
2 hours	-2.9 (-8.81 ; 3.11)	0.3457
3 hours	-3.7 (-10.12 ; 2.72)	0.2559
4 hours	-5.6 (-12.48 ; 1.21)	0.1061
5 hours	-5.7 (-12.84 ; 1.50)	0.1205
6 hours	-5.5 (-13.73 ; 2.70)	0.1864
7 hours	-6.7 (-15.47 ; 1.98)	0.1284
8 hours	-5.4 (-14.08 ; 3.25)	0.2183

5.2 Pharmacokinetic properties

Absorption

Intramuscular injection

After administration of Akis 75 mg/ml Solution for Injection by the i.m. route, absorption is rapid and the mean peak plasma concentration of 2.603 ± 0.959 µg/ml (2.5 ug/ml equals approximately 8 µmol/L) is reached after 34 minutes. The area under the concentration curve AUC_{o-t} is 250.07 ± 46.89 µg/ml.min. In comparative clinical studies the mean peak plasma concentration for intramuscular Voltarol (75mg/3ml) is 2.242 ± 0.566 µg/ml which is reached after 27 minutes and the AUC_{o-t} is 246.70± 39.74 µg/ml.min. The AUC after i.m. administration is about twice as large as it is following oral or rectal administration as this route avoids "first-pass" metabolism.

Subcutaneous injection

After administration of Akis 75 mg/ml Solution for Injection by the s.c. route, absorption is rapid and the mean peak plasma concentrations of 2.138 ± 0.646 µg/ml (2.5 µg/ml equals approximately 8 µmol/l) is reached in 40 minutes. The AUC_{o-t} is 261.94 ± 53.29 µg/ml.min. In comparative clinical studies the mean peak plasma

concentration for intramuscular Voltarol is 2.242 ± 0.566 µg/ml at 27 minutes and the AUC_{o-t} is 246.70 ± 39.74 µg/ml.min. A subcutaneous dose of 75 mg of Akis was bioequivalent to an intramuscularly administered dose of Voltarol 75 mg/3 ml in terms of AUC and C_{max}. The AUC after subcutaneous administration is about twice as large as it is following oral or rectal administration as this route avoids "first-pass" metabolism.

Dose linearity in terms of AUC has been demonstrated for diclofenac absorbed after subcutaneous administration. C_{max} was found to be not proportional to dose, with mean C_{max} values of 1090 ng/ml, 1648.9 ng/ml and 1851.1 ng/ml with the 25 mg, 50 mg and 75 mg dose of Akis respectively.

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 the 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.

Biotransformation

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 ± 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 in the form of 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.

Characteristics in patients

Elderly: No relevant age-dependent differences in the drug's absorption, metabolism or excretion have been observed.

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 <10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

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

No new preclinical safety studies have been performed on sodium diclofenac. The safety profile of the medicinal product is well-established.

The local tolerance study demonstrated that the formulation does not present any significant unexpected local toxicity by either the intramuscular or subcutaneous routes of administration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylbetadex,

Polysorbate 20

Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

The medicinal product must be used immediately after opening any remaining solution must be discarded.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze.

Store in the original packaging in order to protect from light.

6.5 Nature and contents of container

Transparent type I glass ampoule.

Package of 1, 3 and 5 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

An additional overfill is included in each ampoule to ensure that 1.0 mL of solution can be extracted.

Ampoules:- No special requirements.

The product should not be used if crystals or precipitates are observed.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

IBSA Farmaceutici Italia Srl

Via Martiri di Cefalonia 2

26900 Lodi (Italy)

8 MARKETING AUTHORISATION NUMBER(S)

PL 21039/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/11/2012

10 DATE OF REVISION OF THE TEXT

30/09/2016