ACECLOFENAC SYSTEMIC –
AGREED CORE SAFETY PROFILE – 27 DEC 2011
PROCEDURE: HU/H/PSUR/0030/001

4.3. CONTRAINDICATIONS

• Patients with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
• Patients with active bleedings or bleeding disorders
• Patients with severely impaired hepatic or renal organ function
• Patients with severe heart failure
• Pregnancy, especially during the last three months, unless there are compelling reasons for doing so. In this case, the lowest effective dosage should be used (see section 4.6)
• Patients previously sensitive to aceclofenac or to any of the excipients of the product or in whom acetylsalicylic acid or NSAIDs precipitate attacks of asthma, acute rhinitis or urticaria or who are hypersensitive to these drugs.

4.4. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

The use of aceclofenac with other concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Gastrointestinal:

Close medical surveillance is needed in patients with the following conditions as these may be exacerbated (see section 4.8):
• Symptoms indicative of gastrointestinal disorders involving either the upper or lower gastrointestinal tract
• A history suggestive of gastrointestinal ulceration, bleeding or perforation.
• Ulcerative colitis
• Crohn's disease
• Haematological abnormalities

GI bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs at anytime 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 systemic 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 aceclofenac, the treatment should be withdrawn.

Hypersensitivity and skin reactions:
As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug. 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 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Aceclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can trigger serious cutaneous and soft tissues infections complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of aceclofenac in case of varicella

Renal:
The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, liver dysfunction, those being treated with diuretics or recovering from major surgery, and the elderly.

Patients with mild to moderate renal impairment 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 regularly. Effects on renal function are usually reversible on withdrawal of aceclofenac.

Hepatic:
Close medical surveillance is needed in patients suffering from mild to moderate hepatic function impairment.

Aceclofenac should be discontinued if abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash). Hepatitis may occur without prodromal symptoms.

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

Cardiovascular and cerebrovascular:
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 NSAIDs therapy.

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

Aceclofenac should also be administered with caution and under close medical surveillance to patients with a history of cerebrovascular bleeding.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for aceclofenac.

Haematological:
Aceclofenac may reversibly inhibit platelet aggregation (see section 4.5, anticoagulants under 'Interactions').

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.

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).

Long term treatment:
All patients who are receiving long-term treatment with NSAIDs should be monitored as a precautionary measure (e.g. renal, hepatic function and blood counts).

4.5. INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

Lithium and digoxin: Several NSAID drugs inhibit the renal clearance of lithium, resulting in increased serum concentrations of both. The combination should be avoided unless frequent monitoring of lithium and digoxin levels can be performed.

Diuretics: Aceclofenac, like other NSAIDs, may inhibit the activity of diuretics. Although it was not shown to affect blood pressure control when co-administered with bendrofluazide, interactions with other diuretics cannot be ruled out. When concomitant administration with potassium sparing diuretics is employed, serum potassium should be monitored.

Antihypertensives: NSAIDs may reduce the effect of antihypertensives. The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when ACE- inhibitors or angiotensin II receptor antagonists are combined with NSAIDs. 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.

Anticoagulants: Like other NSAIDs, aceclofenac may enhance the activity of anticoagulants. Close monitoring of patients on combined anticoagulant and aceclofenac therapy should be undertaken.

Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): combined with NSAIDs may increase the risk of gastrointestinal bleeding (see section 4.4).

Anti-diabetic agents: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects. Thus with aceclofenac, consideration should be given to adjustment of the dosage of hypoglycaemic agents.

Methotrexate: The possible interaction between NSAIDs and methotrexate should be born in mind also when low doses of methotrexate are used, especially in patients with decreased renal function. When combination therapy has to be used, the renal function should be monitored. Caution should be exercised if both an NSAID and methotrexate are administered within a 24-hour period, since the methotrexate levels may increase and result in increased toxicity.

Other NSAIDs: Concomitant therapy with acetylsalicylic acid and other NSAIDs may increase the frequency of side effects.

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

Ciclosporin, tacrolimus: Administration of NSAID drugs together with cyclosporin or tacrolimus is thought to increase the risk of nephrotoxicity due to decreased synthesis of prostacyclin in the kidney. During combination therapy it is therefore important to carefully monitor renal function.

Zidovudine: When NSAIDs are given with zidovudine there is an increased risk of haematological toxicity. There are indications of an increased risk of haemoarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6. FERTILITY, PREGNANCY AND LACTATION

Pregnancy: There is no information on the use of aceclofenac during pregnancy. Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Data from epidemiological studies suggest an increased risk of miscarriage, cardiac malformation or gastroschisis after use of 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, aceclofenac should not be given unless clearly necessary. If aceclofenac 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, aceclofenac is contraindicated during the third trimester of pregnancy (see section 4.3).

Lactation: There is no information on the secretion of aceclofenac to breast milk; there was however no notable transfer of radio labelled (14C) aceclofenac to the milk of lactating rats.

The use of aceclofenac should therefore be avoided in pregnancy and lactation unless the potential benefits to the mother outweigh the possible risks to the foetus.

Fertility: NSAIDs may impair fertility and are not recommended in women trying to conceive. The temporary discontinuation of aceclofenac should be considered in women having difficulties to conceive or undergoing investigations for infertility.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients suffering from dizziness, vertigo, or other central nervous system disorders whilst taking NSAIDs should refrain from driving or handling dangerous machinery.

4.8. UNDESIRABLE EFFECTS

Exceptionally, occurrence of serious cutaneous and soft tissues infections complications during varicella has been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses 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).

The following is a table of adverse reactions reported from clinical trials and post-authorisation use of aceclofenac, grouped by System-Organ Classes and estimated frequencies. Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1.000 to <1/100), rare (≥1/10.000 to <1/1.000), very rare (<1/10.000).

MedDRA SOC	Common ≥1/100 to <1/10	Uncommon ≥1/1.000 to <1/100	Rare ≥1/10.000 to <1/1.000	Very rare <1/10.000
Blood and lymphatic system disorders			Anaemia	Bone Marrow depression Granulocytopenia Thrombocytopenia Haemolytic Anaemia
Immune system disorders			Anaphylactic reaction (including shock) Hypersensitivity	
Psychiatric disorders				Depression Abnormal dreams Insomnia
Nervous system disorders	Dizziness			Paraesthesia Somnolence Headache Dysgeusia (abnormal taste)
Eye disorders			Visual disturbance	
Ear and labyrinth disorders				Vertigo Tinnitus
Cardiac disorders			Cardiac Failure	Palpitations
Vascular disorders			Hypertension	Flushing Hot flush Vasculitis
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Bronchospasm
Gastrointestinal disorders	Dyspepsia Abdominal pain Nausea Diarrhoea	Flatulence Gastritis Constipation Vomiting Mouth ulceration	Melaena Gastrointestinal haemorrhage Gastrointestinal ulceration	Stomatitis Intestinal perforation Exacerbation of Crohn's disease and Colitis Ulcerative Pancreatitis Haematemesis
Skin and subcutaneous tissue disorders		Pruritus Rash Dermatitis Urticaria	Angioedema	Purpura Severe mucocutaneous skin reaction (including Stevens Johnson Syndrome and

				Toxic Epidermal Necrolysis)
Renal and urinary disorders		Blood urea increased Blood creatinine increased		Nephrotic syndrome Renal Failure
Hepatobiliar disoders	Hepatic enzyme increased			Hepatic injury (including hepatitis) Blood alkaline phosphatase increased
General disorders and administration site conditions				Oedema Fatigue
Investigations				Weight increase

See 4.4 and 4.5 for Warnings, Precautions and Interactions.

4.9. OVERDOSE

There is insufficient data available on the consequences of aceclofenac overdose in humans.

The treatment of acute poisoning by non-steroid anti-inflammatory drugs basically consists of supportive and symptomatic treatment for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation, and respiratory depression.

Management of acute poisoning with oral aceclofenac consists of preventing absorption as soon as possible after ovedose by means of gastric lavage and treatment with activated charcoal.

Given the route of administration and the pharmaceutical form, an overdose with injectable aceclofenac is unlikely.

Forced diuresis, dialysis or haemoperfusion may not be able to eliminate NSAIDs due to their high rate of protein binding and extensive metabolism.

ACECLOFENAC CREAM – AGREED CSP – 27 DEC 2011

4.3. CONTRAINDICATIONS

Patients known to suffer hypersensitivity. Even though possible cross hypersensitivity with Diclofenac has not been established, administration is not recommended in those patients that have demonstrated hypersensitivity to Diclofenac.

Patients previously sensitive to aceclofenac or to any of the excipients of the product or in whom acetylsalicylic acid or NSAIDs precipitate attacks of asthma, acute rhinitis or urticaria or who are hypersensitive to these drugs.

It is not to be used in patients that are allergic to any of the components of the cream.

4.4. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

If the use of aceclofenac cream produces symptoms of local irritation administration must be suspended and suitable therapeutic treatment established. It must not be applied to the eyes or other mucous membrane, nor on open lesions of the skin or under any other circumstance where the application site involves any other cutaneous process.

The safety and efficacy of aceclofenac in children up to 14 years old have not been established yet. No data are available.

Avoid unprotected exposure of the treated area to strong sunlight to prevent photosensitivity reactions.

Hypersensitivity and skin reactions: As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug. 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 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Aceclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can trigger serious cutaneous and soft tissues infections complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of aceclofenac in case of varicella

4.5. INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

Although information is still not available on interactions of aceclofenac cream, caution is recommended when used with lithium, digoxin, oral anticoagulant agents, diuretics and pain-killers.

4.6. FERTILITY, PREGNANCY AND LACTATION

Although teratogenic effects were not observed in the experimental studies, the safety of aceclofenac in pregnant and nursing mothers has not been established, therefore administration is not recommended in these situations.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None expected.

4.8. UNDESIRABLE EFFECTS

The most commonly reported adverse reactions are moderate or mild local irritation accompanied by reddening and mild pruritus that disappears with interruption of treatment.

Exceptionally, occurrence of serious cutaneous and soft tissues infections complications during varicella has been reported in association with NSAID treatment.

There have been occasional reports of photosensitivity reactions when treated skin areas have been exposed to strong sunlight without adequate protection.

The following is a table of adverse reactions reported from clinical trials and post-authorisation use of aceclofenac, grouped by System-Organ Classes and estimated frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1.000 to <1/100), rare (≥1/10.000 to <1/1.000), very rare (<1/10.000).

MedDRA SOC	Common ≥1/100 to <1/10	Uncommon ≥1/1.000 to <1/100	Rare ≥1/10.000 to <1/1.000	Very rare <1/10.000
Skin and subcutaneous tissue disorders		Photosensitivity, erythema, pruritus.		Bullous reactions (including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis)

4.9. OVERDOSE

In the unlikely event of an overdose, treat symptomatically.