PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE:
AUSTELL DICLOFENAC SODIUM 25 mg/mL INJECTION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

AUSTELL DICLOFENAC SODIUM 25 mg/mL INJECTION.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 25 mg diclofenac sodium (75 mg/3 mL ampoule)

Excipients(s) with known effect:

Preservative: Benzyl alcohol 4 % *m/v*

Antioxidant: Sodium metabisulphite 0,3 % *m/v*

Sugar free: contains mannitol 0,6 % *m/v*

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in ampoules.

A clear, colourless to almost colourless solution free from any particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AUSTELL DICLOFENAC 25 mg/mL Injection (75 mg/3 mL Ampoule)

Use for intramuscular injection only: For initial therapy of inflammatory and degenerative rheumatic diseases, as well as the treatment of mild to moderately painful conditions due to inflammation of non–rheumatic origin.

4.2 Posology and method of administration

Posology

Adults

The maximum total daily dose of AUSTELL DICLOFENAC SODIUM 25 mg/mL by any route is 150 mg.

Paediatric population

Because of the dosage strength, AUSTELL DICLOFENAC is not suitable for use in children and adolescents below 14 years of age (see section 4.3).

Method of administration

Adults

AUSTELL DICLOFENAC should not be given as an intravascular injection.

Intramuscular injection

AUSTELL DICLOFENAC is given by deep intra-muscular injection into the gluteal muscle in a dose of 75 mg once daily or, if required in severe conditions, 75 mg twice daily. The directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissues at the injection site. After inserting the needle the plunger should be pulled back to avoid inadvertent intra-arterial injection. Each injection to be given at a different site.
Use the lowest effective dose for the shortest possible duration of treatment.
AUSTELL DICLOFENAC should not be given for more than 2 days, if necessary, the treatment can be continued with oral or rectal formulation.

4.3 Contraindications

- AUSTELL DICLOFENAC is contraindicated in patients with hypersensitivity to diclofenac sodium or any of the other ingredients (see section 6.1).
- AUSTELL DICLOFENAC is also contraindicated in patients in whom attacks of asthma, urticaria, angioedema, heart failure or rhinitis are precipitated by acetylsalicylic acid or by other NSAIDs.
- AUSTELL DICLOFENAC should not be given to patients with gastric or intestinal ulcers, bleeding or perforation.
- AUSTELL DICLOFENAC is contraindicated in patient with a history of gastro-intestinal bleeding, ulceration or perforation (PUBs) related to previous NSAIDs.
- AUSTELL-DICLOFENAC is contraindicated in patients with active or history of recurrent ulcer/haemorrhage/perforations.
- AUSTELL DICLOFENAC is contraindicated in patients with bleeding disorders.
- AUSTELL DICLOFENAC is not recommended for children (see section 4.2).
- Pregnant women from around 20 weeks of gestation or later in pregnancy (see section 4.4 and 4.6).
- Lactation (see section 4.6)
- AUSTELL DICLOFENAC should not be used in patients with porphyria.

4.4 Special warnings and precautions for use

General

Strict accuracy of diagnosis and close medical surveillance are imperative in patients with symptoms indicative of gastro-intestinal disease, a case history suggestive of gastro-intestinal ulceration, ulcerative colitis, Crohn's disease, in patients suffering from impaired hepatic function and pre-existing dyshaemopoiesis or disorders of blood coagulation.

Patients undergoing therapy may need to be monitored for development of blood, kidney, liver or eye disorders.

Diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Renal impairment

AUSTELL DICLOFENAC should be administered with caution to patients with renal impairment. Renal papillary necrosis and nephritic syndrome have been reported in patients taking diclofenac.

Hepatic effects

AUSTELL DICLOFENAC should also be administered with caution in patients with hepatic impairment. Increase of serum aminotransferase activity, clinical hepatitis, including fatal fulminant hepatitis have been reported. Patients using AUSTELL DICLOFENAC for osteoarthritis are at a risk of hepatotoxicity.

Cardiovascular effects

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with AUSTELL DICLOFENAC therapy.

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastro-intestinal bleeding and perforation (PUBs) which may be fatal. AUSTELL DICLOFENAC should be used with caution in the elderly, and AUSTELL DICLOFENAC may have to be given in

reduced doses in such patients.

Gastrointestinal effects

The risk of gastro-intestinal bleeding or perforation (PUBs) is higher with increasing doses of AUSTELL DICLOFENAC, in patients with a history of ulcers, and the elderly. When gastro-intestinal bleeding or ulceration occurs in patients receiving AUSTELL DICLOFENAC, treatment with AUSTELL DICLOFENAC should be stopped. AUSTELL DICLOFENAC should be given with caution to patients with a history of gastro-intestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

Skin effects

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. AUSTELL DICLOFENAC should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Also refer to DRESS syndrome below.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS)

DRESS has been reported in patients taking NSAIDs such as AUSTELL DICLOFENAC. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity,

such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue AUSTELL DICLOFENAC and evaluate the patient immediately.

Risk of foetal renal dysfunction and foetal ductus arteriosus

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) around 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Oligohydramnios is often, but not always, reversable with treatment discontinuation. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation (see section 4.3 and 4.6). Invasive procedures such as exchange transfusion or dialysis may be required.

If NSAID treatment is deemed necessary between 20 to 30 weeks of pregnancy, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours. Discontinue the NSAID if oligohydramnios occurs and follow up according to clinical practice (see section 4.3 and 4.6).

Avoid prescribing NSAIDs at 30 weeks and later in pregnancy because of the additional risk of premature closure of the foetal ductus arteriosus (see section 4.6).

Excipient(s) with known effect

AUSTELL DICLOFENAC contains 600 mg propylene glycol per 3 mL ampoule which is equivalent to 200 mg/mL.

AUSTELL DICLOFENAC contains 120 mg benzyl alcohol per 3 mL ampoule which is equivalent to 40 mg/mL. Benzyl alcohol may cause allergic reactions. Ask your doctor or pharmacist for advice if you are pregnant or breastfeeding or if you have liver or kidney

disease. This is because large amounts of benzyl alcohol can build up in your body and may cause side effects (called 'metabolic acidosis').

The sodium metabisulphite present in AUSTELL DICLOFENAC may cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicines and other forms of interaction

Lithium or digoxin

When given together with preparations containing lithium or digoxin, AUSTELL DICLOFENAC may raise their plasma concentrations.

Corticosteroids or other NSAIDs

Concomitant administration of glucocorticoids and other non-steroidal anti-inflammatory agents may aggravate gastro-intestinal side effects.

Concurrent treatment with two or more non-steroidal anti-inflammatory (NSAIDs) agents may increase the occurrence of side–effects.

The bioavailability of AUSTELL DICLOFENAC is reduced by aspirin and that of aspirin by AUSTELL DICLOFENAC when the two agents are administered together.

Anticoagulants and anti-platelets

Increased risk of haemorrhage has been reported when AUSTELL DICLOFENAC has been used in combination with anticoagulant- and anti-platelet therapy. AUSTELL DICLOFENAC may enhance the effects of anti-coagulants such as warfarin.

Antidiabetics

Both hypoglycaemic and hyperglycaemic effects in the presence of AUSTELL DICLOFENAC, which necessitated changes in the dosage of hypoglycaemic agents have been reported.

Ciclosporin

Increased nephrotoxicity of ciclosporin may occur through effects of AUSTELL DICLOFENAC on renal prostaglandins.

Quinolone antibacterial

There have been isolated reports of convulsions, which may have been due to concomitant use of quinolones and non-steroidal anti-inflammatory drugs (NSAIDs) such as AUSTELL DICLOFENAC.

Selective serotonin reuptake inhibitors (SSRIs)

Concomitant use of NSAIDS and selective serotonin reuptake inhibitors (SSRIs) may increase the risk of gastro-intestinal bleeding (see section 4.4)

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of NSAIDS, such as AUSTELL DICLOFENAC used at 20 weeks gestation or later may cause serious kidney problems in an unborn baby.

After around 20 weeks of pregnancy, the unborn babies' kidneys produce most of the amniotic fluid. Amniotic fluid provides a protective cushion and helps the unborn babies' lungs, digestive system, and muscles develop. Foetal renal dysfunction can lead to oligohydramnios due to the low levels of amnionic fluid. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation (see section 4.2 and 4.4).

Use during the third trimester of pregnancy is contraindicated.

The use of AUSTELL DICLOFENAC during the third trimester of pregnancy may result in closure of the foetal ductus arteriosus in utero, and possible persistent pulmonary hypertension of the newborn.

Breastfeeding

Diclofenac passes into breast milk in small amounts. Therefore, AUSTELL DICLOFENAC should not be administered during breastfeeding in order to avoid undesirable effects in the infant.

Fertility

The use of diclofenac may impair female fertility and is not recommended in woman attempting to conceive. In woman who have difficulties conceiving or who are undergoing investigation of infertility.

4.7 Effects on ability to drive and use machines

Occasionally people have reported that diclofenac sodium injections have made them feel dizzy, tired or sleepy. Problems with eyesight have also been reported. If you are affected in this way, you should not drive or operate machinery.

4.8 Undesirable effects

MedDRA System Organ Class	Frequency		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations		Aseptic meningitis	Injection site necrosis
Blood and lymphatic system disorders		Anaemia, thrombocytopenia, neutropenia, eosinophilia and agranulocytosis	
Immune system disorders	Fever, angioedema, oedema, bronchospasm and rashes	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock) Angioneurotic oedema (including face oedema)	
Psychiatric disorders		Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder	
Nervous system disorders	Headache, vertigo, dizziness, nervousness, tinnitus	Depression, drowsiness and insomnia, paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances,	Confusion, hallucinations, disturbances of sensation, malaise

		cerebrovascular accident	
Eye disorders		Visual disturbances, vision blurred, diplopia	Optic neuritis
Ear and labyrinth disorders	Vertigo	Hearing impaired	
Cardiac disorders		Palpitations, chest pain, hypertension, and congestive cardiac failure	Kounis syndrome
Vascular disorders		Hypertension, hypotension, vasculitis	
Respiratory, thoracic and mediastinal disorders		Alveolitis, pulmonary eosinophilia, asthma (including dyspnoea), pneumonitis	
Gastrointestinal disorders	Gastrointestinal discomfort, nausea, diarrhoea, vomiting, flatulence, dyspepsia, abdominal pain, anorexia	Peptic ulceration, gastrointestinal bleeding and perforation, constipation, melaena, haematemesis, ulcerative stomatitis, gastritis, exacerbation of colitis and Crohn's disease.	Ischaemic colitis
Hepatobiliary disorders	Transaminases increased	Hepatotoxicity, pancreatitis, hepatitis, jaundice, liver disorder, fulminant hepatitis,	

		hepatic necrosis, hepatic failure	
Skin and subcutaneous tissue disorders	Rash	Bullous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolyis and photosensitivity, urticaria, eczema, erythema, erythema multiforme, dermatitis exfoliative, loss of hair, purpura, allergic purpura, pruritus	[a)]Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome
Renal and urinary disorders		Renal failure, nephropathy, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis	
Reproductive system and breast disorders		Impotence	
General disorders and administration site conditions		Pain and tissue damage at the site of injection, oedema	

[a)]Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

General symptoms of nausea, vomiting, headache, drowsiness, blurred vision and dizziness have been reported. There have been isolated case reports of more serious toxicity, including seizures, hypotension, apnoea, coma, and renal failure, although usually after ingestion of substantial quantities.

Treatment is entirely supportive.

Forced diuresis, haemodialysis, or haemoperfusion are unlikely to be of any benefit, although haemodialysis may be required if oliguric renal failure develops. There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 3.1 Anti-Rheumatic (anti-inflammatory agent)

Pharmacotherapeutic group: Nonsteroidal anti-inflammatory drugs (NSAIDs)

ATC Code: M01AB05

Diclofenac has analgesic, antipyretic and anti-inflammatory activities. Diclofenac is an inhibitor of cyclo-oxygenase. It also appears to reduce intracellular concentrations of free arachidonate in leukocytes, by altering the release or uptake of the fatty acids.

5.2 Pharmacokinetic properties

Absorption

Peak plasma concentrations are attained 10 to 20 minutes after an intramuscular dose.

Distribution

Protein binding: 99,7 %

Biotransformation and elimination

Diclofenac is metabolised in the liver by a cytochrome P-450 isozyme of the CYP2C subfamily to 4-hydroxydiclofenac, the principle metabolite, and other hydroxylated forms; after glucuronidation and sulfation, the metabolites are excreted in the urine and bile.

The mean terminal elimination half-life of the unchanged medicine is 1-2 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol, benzyl alcohol, sodium metabisulphite, mannitol, sodium hydroxide, water for injection, 4 % *w/v* sodium hydroxide solution.

6.2 Incompatibilities

The ampoules used should not be mixed with other injection solutions.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

Keep ampoules in carton/polystyrene container until required for use.

6.5 Nature and contents of container

A clear colourless solution free from any particulate matter.

Clear and colourless ampoules of 10 x 3 mL and 50 x 3 mL.

6.6 Special precautions for disposal

None stated.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Austell Laboratories (Pty) Ltd.

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Johannesburg, 2193

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8. REGISTRATION NUMBER

36/3.1/0405

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 17 September 2004

10. DATE OF REVISION OF THE TEXT

Date of revision: 18 March 2022