

## Summary of Product Characteristics for Pharmaceutical Products

### 1. Name of the medicinal product

ZULU-ES Tablet

### 2. Qualitative and quantitative composition

Each film coated tablet contains:

Aceclofenac 100mg

Paracetamol 500mg

Esomeprazole 20mg

For the full list of excipients, see section 6.1.

### 3. Pharmaceutical form

Film coated tablet

A white color oblong shape biconvex film coated tablet, scored in the middle on one side and plain on other side of the table

### 4. Clinical particulars

#### 4.1 Therapeutic indications

Aceclofenac and Paracetamol is indicated for relief of acute to moderate pain and inflammation in Osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, lower back pain, dental pain, gynaecological pain and pain relief in inflammatory conditions associated with the ear, nose & throat. Esomeprazole is used for the treatment of erosive reflux esophagitis.

#### 4.2 Posology and method of administration

For oral administration.

**Adults:** Usual dose is 1 tablet to be administered once daily. The tablet should be swallowed whole with water.

It is not recommended for use in children.

#### 4.3 Contraindications

ZULU-ES Tablets are contraindicated in the following:

- Known hypersensitivity to aceclofenac or to paracetamol or to esomeprazole or to any component of the formulation.
- History of gastrointestinal (GI) bleeding or perforation, relating to previous NSAID therapy.
- Severe heart failure, hepatic failure and renal failure.

- Patients with established congestive heart failure (NYHA class II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease
- During the last trimester of pregnancy.
- Patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by aspirin or other NSAIDs.

#### **4.4 Special warnings and precautions for use**

##### **Aceclofenac**

*Gastrointestinal (GI) 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 dose, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, 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 GI risk. 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. When GI bleeding or ulceration occurs in patients receiving aceclofenac, 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 their condition may be exacerbated. Hypersensitivity Reactions: As with other NSAIDs, allergic reactions (including anaphylactic reactions), can occur without earlier exposure to the drug.

*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. 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.

*Respiratory:* Use with caution in patients suffering from or with a previous history of bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

*Hematological:* Aceclofenac may reversibly inhibit platelet aggregation. Patients with defect of hemostasis, bleeding diathesis or hematological abnormalities should be carefully monitored.

*Hepatic:* Close medical surveillance is also imperative in patients suffering from severe impairment of hepatic function. If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), aceclofenac should be discontinued. Hepatitis may occur without prodromal symptoms. Use of aceclofenac in patients with hepatic porphyria may trigger an attack.

*Renal:* Patients with mild renal or cardiac impairment and the elderly should be kept under surveillance, since the use of NSAIDs may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored regularly. The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of aceclofenac.

*Cardiovascular:* Caution is required in patients with a history of hypertension and/or heart failure, as fluid retention and edema have been reported in association with NSAID therapy. 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 edema have been reported in association with NSAID therapy. 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 (e.g., myocardial infarction or stroke). There are insufficient data to exclude such a risk for aceclofenac. Patients with uncontrolled hypertension, congestive heart failure, established ischemic 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 longer-term treatment of patients with risk factors for cardiovascular disease (e.g., hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

*Fertility:* The use of aceclofenac 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 aceclofenac should be considered.

*Other NSAIDs (Including COX-2 Selective Inhibitors):* The use of aceclofenac with concomitant aspirin/NSAIDs including cyclooxygenase-2 (COX-2) selective inhibitors should be avoided as this may increase the risk of adverse effects including the risk of GI bleeding.

*Long Term Treatment:* Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. As a precautionary measure, all patients who are receiving NSAIDs for longer time should be regularly monitored for renal failure, hepatic function and blood counts.

### **Paracetamol**

*Hepatotoxicity:* Significant overdose of paracetamol can lead to hepatotoxicity in some patients. Thus, do not exceed the recommended dose. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

*Other Paracetamol-Containing Products:* Do not take with any other paracetamol-containing products, so as to avoid the chances of overdose.

*Renal and Hepatic Impairment:* Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment.  
*Alcohol:* Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive paracetamol use, although rarely.

### **Esomeprazole**

#### *Gastrointestinal infections*

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter.

#### *Absorption of vitamin B12*

Esomeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

#### *Hypomagnesaemia*

Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) like esomeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

#### *Risk of fracture*

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other

recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

##### **Aceclofenac**

*Lithium:* Aceclofenac, like many NSAIDs, may increase plasma concentration of lithium and thus, increases their risk of its toxicity.

*Cardiac Glycosides (Digoxin):* Through their renal effects, NSAIDs may increase plasma glycoside levels, exacerbate cardiac failure and reduce the glomerular filtration rate (GFR) in patients receiving glycosides.

*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. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

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

*Antihypertensive Drugs:* 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 angiotensin converting enzyme (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.

*Antidiabetic 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 hypoglycemic and hyperglycemic effects. Thus, with aceclofenac, consideration should be given to adjustment of the dosage of hypoglycemic agents.

*Methotrexate:* Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other, since NSAIDs may increase plasma levels, resulting in increased toxicity.

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

*Corticosteroids:* Concomitant administration of aceclofenac with corticosteroids may increase the risk of GI ulceration or bleeding.

*Anti-Platelet Agents and Selective Serotonin Reuptake Inhibitors (SSRIs):* Concomitant administration of aceclofenac with these drugs may increase the risk of GI bleeding.

*Ciclosporin:* Ciclosporin nephrotoxicity may be increased by the effect of NSAIDs on renal prostaglandins.

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

### **Paracetamol**

*Cholestyramine:* The rate of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour, if maximal analgesia is required.

*Metoclopramide and Domperidone:* The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

*Warfarin:* The anti-coagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

*Chloramphenicol:* Concurrent administration of paracetamol and chloramphenicol may markedly retard the elimination of chloramphenicol and thus, increases plasma concentration of chloramphenicol which leads to risk of its harmful effects. Monitoring of chloramphenicol plasma levels is recommended while combining paracetamol with chloramphenicol injection.

*Alcohol, Anticonvulsants, and Isoniazid:* Concomitant administration of alcohol, anticonvulsants, and isoniazid with paracetamol may increase risk of hepatotoxicity.

### **Esomeprazole**

*Effects of esomeprazole on the pharmacokinetics of other medicinal products*

Medicinal products with pH dependent absorption

Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal

products such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects). Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

#### *Protease inhibitors*

Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP 2C19.

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC,  $C_{max}$  and  $C_{min}$ ). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg qd) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg qd without omeprazole 20 mg qd. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC,  $C_{max}$  and  $C_{min}$  by 36-39 % and mean AUC,  $C_{max}$  and  $C_{min}$  for the pharmacologically active metabolite M8 was reduced by 75-92%. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended (see section 4.4) and concomitant administration with esomeprazole and nelfinavir is contraindicated (see section 4.3).

For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg qd). Treatment with omeprazole 20 mg qd had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir). Treatment with esomeprazole 20 mg qd had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg qd had no effect on the exposure of lopinavir (with concomitant ritonavir).

#### *Methotrexate*

When given together with PPIs, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

#### *Tacrolimus*

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and dosage of tacrolimus adjusted if needed.

#### *Medicinal products metabolised by CYP2C19*

Esomeprazole inhibits CYP2C19, the major esomeprazole-metabolising enzyme. Thus, when esomeprazole is combined with medicinal products metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these medicinal products may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on-demand therapy.

#### *Diazepam*

Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam.

#### *Phenytoin*

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

#### *Voriconazole*

Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate)  $C_{max}$  and AUC by 15% and 41%, respectively.

#### *Warfarin*

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical trial showed that coagulation times were within the accepted range. However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

#### *Cilostazol*

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased  $C_{max}$  and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.



### Cisapride

In healthy volunteers, concomitant administration of 40 mg esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ( $t_{1/2}$ ) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see also section 4.4).

### Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic (PK)/ pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40mg p.o.daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution concomitant use of clopidogrel should be discouraged.

In a crossover clinical study, clopidogrel (300 mg loading dose followed by 75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) was diminished by 47% (24 hours) and 30% (Day 5) when clopidogrel and omeprazole were administered together. In another study it was shown that administering clopidogrel and omeprazole at different times did not prevent their interaction that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19. Inconsistent data on the clinical implications of this PK/PD interaction in terms of major cardiovascular events have been reported from observational and clinical studies.

## **4.6 Fertility, pregnancy, and lactation**

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

#### **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, including aceclofenac. Thus, patients are advised not to drive vehicles or operate machinery while taking this medicine.

#### **4.8 Undesirable effects**

##### **Aceclofenac**

The majority of adverse reactions reported have been reversible and of a minor nature. The most frequent are GI disorders, in particular dyspepsia, abdominal pain, nausea and diarrhoea, and occasional dizziness. If serious adverse reactions occur, aceclofenac should be withdrawn. Gastrointestinal: The most commonly observed adverse events are GI in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely. Hypersensitivity: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of a non-specific allergic reaction and/or anaphylaxis or respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnea. Cardiovascular and Cerebrovascular: Edema, hypertension, palpitation, flushing, hot flushes, vasculitis and cardiac failure have 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 an increased risk of arterial thrombotic events (e.g., myocardial infarction or stroke). Neurological and Special Senses: Optic neuritis, somnolence, reports of aseptic meningitis (especially in patients with existing auto immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease) with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation, malaise, confusion, and drowsiness. Renal: Interstitial nephritis. Hematological: Agranulocytosis, aplastic anaemia. Miscellaneous: In patients with varicella, serious cutaneous and soft tissue infections have been reported in association with NSAID treatment. Other rarely reported adverse reactions of aceclofenac include the following: Renal and Urinary: Renal insufficiency, abnormal serum creatinine levels, increased blood urea, renal failure, nephrotic syndrome. Respiratory: Dyspnea, bronchospasm, stridor. Hepatic: Abnormal hepatic enzyme levels, hepatitis, jaundice, increased blood alkaline phosphatase. Blood and Lymphatic System: Anemia, bone marrow depression, granulocytopenia, thrombocytopenia, neutropenia, hemolytic anemia. Skin and Subcutaneous Tissue Disorders: Pruritus, rash,

photosensitivity reactions, dermatitis urticaria, angioedema, purpura, erythema multiforme, exfoliative dermatitis, bullous dermatoses, severe mucocutaneous skin reactions (including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis) Ear and Labyrinth Disorders: Tinnitus, vertigo. Eye Disorders: Visual disturbance. Nervous System: Paraesthesia, tremor, somnolence, headache, dysgeusia. Psychiatric Disorders: Depression, abnormal dreams, confusion, hallucinations, insomnia. Metabolism: Hyperkalemia. General Disorders: Edema, fatigue, leg cramps.

### **Paracetamol**

Adverse effects of paracetamol are rare. However, hypersensitivity including skin rash and fixed drug eruption (FDE) may occur. There have been reports of blood dyscrasias including thrombocytopenic purpura, methemoglobinemia and agranulocytosis, but these were not necessarily related to paracetamol.

### **Esomeprazole**

<b>System Organ Class</b>	<b>Frequency</b>	<b>Undesirable Effect</b>
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia
	Very rare	Agranulocytosis, pancytopenia
Immune system disorders	Rare	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders	Uncommon	Peripheral oedema
	Rare	Hyponatraemia
	Not known	Hypomagnesaemia (see section 4.4); severe hypomagnesaemia can correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.
Psychiatric disorders	Uncommon	Insomnia
	Rare	Agitation, confusion, depression
	Very rare	Aggression, hallucinations
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, paraesthesia, somnolence
	Rare	Taste disturbance
Eye disorders	Rare	Blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm
Gastrointestinal disorders	Common	Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting, fundic gland polyps (benign)
	Uncommon	Dry mouth
	Rare	Stomatitis, gastrointestinal candidiasis
	Not known	Microscopic colitis

Hepatobiliary disorders	Uncommon	Increased liver enzymes
	Rare	Hepatitis with or without jaundice
	Very rare	Hepatic failure, encephalopathy in patients with pre-existing liver disease
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, pruritus, rash, urticaria
	Rare	Alopecia, photosensitivity
	Very rare	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS)
	Not known	Subacute cutaneous lupus erythematosus (see section 4.4).
Musculoskeletal and connective tissue disorders	Uncommon	Fracture of the hip, wrist or spine (see section 4.4)
	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
Renal and urinary disorders	Very rare	Interstitial nephritis; in some patients renal failure has been reported concomitantly.
Reproductive system and breast disorders	Very rare	Gynaecomastia
General disorders and administration site conditions	Rare	Malaise, increased sweating

**Reporting of suspected adverse reactions:** Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

#### 4.9 **Overdose** **Aceclofenac**

**Symptoms:** There are no human data available on the consequences of aceclofenac overdose. Symptoms of overdose include headache, nausea, vomiting, epigastric pain, GI irritation, GI bleeding. Rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, hypotension, respiratory depression, fainting, and occasionally convulsions may occur. In cases of significant poisoning acute renal failure and liver damage are possible.

**Treatment:** If overdose with aceclofenac occurs, absorption should be prevented as soon as possible by means of gastric lavage and treatment with activated charcoal. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, GI irritation, and respiratory depression. Specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism. Renal and liver function should be closely monitored.

## **Paracetamol**

Symptoms: Ingestion of 5 gram or more of paracetamol may lead to liver damage. Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, hemorrhage, hypoglycaemia, cerebral edema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, hematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

**Treatment:** Immediate treatment is essential in the management of paracetamol overdose. Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine (approved antidote) may be used up to 24 hours after ingestion of paracetamol. However, the maximum protective effect is obtained up to 8 hours post ingestion.

## **Esomeprazole**

There is very limited experience to date with deliberate overdose.

### Symptoms

The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful.

### Management

No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

## **5. Pharmacological properties**

### **5.1 Pharmacodynamic properties**

**Aceclofenac** ATC code: M01A B16

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) with marked analgesic and antiinflammatory properties

The mode of action of aceclofenac is largely based on the inhibition to prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase (COX). COX enzymes are involved in conversion of arachidonic acid into prostaglandin (PGs). Prostaglandins are usually responsible for causing pain, inflammation, and fever. Aceclofenac blocks the enzyme COX and thereby inhibit PGs synthesis, thus, produces analgesic and anti-inflammatory effects.

**Paracetamol** ATC Code: N02 BE01

Paracetamol is a centrally acting analgesic and antipyretic agent.

*Analgesic Effect:* The mechanism of analgesic action of paracetamol has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent, through a peripheral action by blocking painimpulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

*Antipyretic Effect:* Paracetamol produces antipyretic effect by acting centrally on the hypothalamic heat-regulation center to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action involves inhibition of prostaglandin synthesis in the hypothalamus.

**Esomeprazole** ATC Code: A02B C05

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.

Mechanism of action

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H<sup>+</sup>K<sup>+</sup>-ATPase – the acid pump and inhibits both basal and stimulated acid secretion.

Pharmacodynamic effects

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GERD patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for esomeprazole 20 mg 76%, 54% and 24%. Corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

Therapeutic effects of acid inhibition

Healing of reflux esophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks.

One week treatment with esomeprazole 20 mg b.i.d. and appropriate antibiotics, results in successful eradication of *H. pylori* in approximately 90% of patients.

After eradication treatment for one week, there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

In a randomized, double blind, placebo-controlled clinical study, patients with endoscopically confirmed peptic ulcer bleeding characterised as Forrest Ia, Ib, IIa or IIb (9%, 43%, 38% and 10 % respectively) were randomized to receive esomeprazole solution for infusion (n=375) or placebo (n=389). Following endoscopic haemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for 72 hours. After the initial 72 hour period, all patients received open-label 40 mg oral esomeprazole for 27 days for acid suppression. The occurrence of rebleeding within 3 days was 5.9% in the esomeprazole treated group compared to 10.3% for the placebo group. At 30 days post-treatment, the occurrence of rebleeding in the esomeprazole treated versus the placebo treated group was 7.7% vs 13.6%.

#### Other effects related to acid inhibition

During treatment with antisecretory medicinal products serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in both children and adults during long term treatment with esomeprazole. The findings are considered to be of no clinical significance.

During long-term treatment with antisecretory medicinal products, gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead

to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

#### Clinical efficacy and safety

In two studies with ranitidine as an active comparator, esomeprazole showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs.

In two studies with placebo as comparator, esomeprazole showed better effect in the prevention of gastric and duodenal ulcers in patients using NSAIDs (aged >60 and/or with previous ulcer), including COX-2 selective NSAIDs.

#### Paediatric population

In a study in paediatric GERD patients (<1 to 17 years of age) receiving long-term PPI treatment, 61% of the children developed minor degrees of ECL cell hyperplasia with no known clinical significance and with no development of atrophic gastritis or carcinoid tumour

## **5.2 Pharmacokinetic properties**

### **Aceclofenac**

After oral administration, aceclofenac is rapidly and completely absorbed as unchanged drug. Peak plasma concentrations are reached approximately 1.25 to 3.00 hours following ingestion. Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 57% of those in plasma. The volume of distribution is approximately 25 liters. The mean plasma elimination half-life is around 4 hours. Aceclofenac is highly protein-bound (>99%). Aceclofenac circulates mainly as unchanged drug. The main metabolite detected in plasma is 4'-hydroxyaceclofenac. Approximately two-thirds of the administered dose is excreted via the urine, mainly as hydroxymetabolites. No changes in the pharmacokinetics of aceclofenac have been detected in the elderly.

### **Paracetamol**

Paracetamol is readily absorbed from the GI tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. Paracetamol is metabolized in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

### **Esomeprazole**

#### *Absorption*



*In vivo* conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68%, respectively.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

#### *Distribution*

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 l/kg body weight. Esomeprazole is 97% plasma protein bound.

#### *Biotransformation*

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

#### *Elimination*

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 l/h after a single dose and about 9 l/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once daily dosing. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

### **5.3 Preclinical safety data**

No data available.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Maize Starch  
Microcrystalline Cellulose  
Povidone K30  
Colloidal Anhydrous Silica

Magnesium Stearate  
Eudragit L30d 55  
Tab Coat White  
Isopropyl Alcohol  
Dichloromethane  
Purified Water

**6.2 Incompatibilities**

None known

**6.3 Shelf life**

24 months

**6.4 Special precautions for storage:**

Store in a dry place below 30°C. Protect from light.

**6.5 Nature and contents of container**

Packed in one PVC-Blister and one PVC-Blister is kept in one carton along with package insert

Pack size 4's, 10's, 20's, 30's & 100's

**6.6 Special precautions for disposal and other handling:**

No special requirements

**7. Marketing authorization holder and manufacturing site addresses**

**Marketing authorization holder:**

Innocia Lifesciences Pvt. LTD.,

**Manufacturing site address:**

Atoz Pharmaceuticals Pvt Ltd

New no. 12, Balaji Nagar, Ambattur, Chennai - 600053 India

**8. Marketing authorization number**

CTD9636

**9. Date of first registration**

13/03/2023

**10. Date of revision of the text:**

17/09/2023

**11. Dosimetry:**

Not Applicable

**12. Instructions for Preparation of Radiopharmaceuticals:**

Not Applicable