PRODUCT MONOGRAPH

WILLGO

Aceclofenac 100mg + Paracetamol 325mg

Oral Administration

Analgesic / Antipyretic / Anti-inflammatory drugs

Manufactured By:

Panacea Biotec Limited.

Tehshil Nalagarh,

Distt. Solan(H.P) – 173205, India

Date of Preparation:

(24-07-2019)Malpur, Baddi,

Willgo

Aceclofenac 100mg + Paracetamol 325mg

Oral Administration

Analgesic / Antipyretic / Anti-inflammatory drugs

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	**Dosage Form / Strength**	**Approved Indications**
Oral	Tablets Aceclofenac 100 mg Paracetamol 500 mg	Indicated for acute painful condition in adults.
Oral	Capsule Aceclofenac SR 200mg Thiocolchicoside SR 8mg	Indicated for symptomatic relief of musculoskeletal pain with associated spasm

INDICATIONS AND CLINICAL USE

- Oedema and swelling
- Joint pains and trauma
- Dental pain
- Post-operative pain
- Pelvic inflammatory disease
- Deep Epiosiotomy
- Caesearian cases

CONTRAINDICATIONS

RF - Willgo is contraindicated in the following situations:

· Patients sensitive to Aceclofenac, Paracetamol or to any of the excipients of the product

· Patients in whom aspirin or other NSAIDs, precipitate attacks of bronchospasm, acute rhinitis or urticaria or patients hypersensitive to these drugs

· Patients with active or suspected peptic ulcer or gastrointestinal bleeding or bleeding disorders

· Patients with severe heart failure, hypertension, hepatic or renal insufficiency

· Third trimester of pregnancy

WARNINGS AND PRECAUTIONS

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. The use of with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Aceclofenac

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

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.

Cardiovascular, Renal and Hepatic Impairment: The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients.

Renal: 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.

Hepatic: 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. Close medical surveillance is necessary in patients suffering from mild to moderate impairment of hepatic function. Hepatitis may occur without prodromal symptoms. Use of aceclofenac in patients with hepatic porphyria may trigger an attack.

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 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.

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 longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

Gastrointestinal Bleeding, Ulceration and Perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any

time during treatment, with or without warning symptoms or a previous history of serious GI events.

Close medical surveillance is imperative in patients with symptoms indicative of gastro-intestinal disorders, with a history suggestive of gastrointestinal ulceration, with ulcerative colitis or with Crohn's disease, bleeding diathesis or haematological abnormalities.

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, 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.

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 antiplatelet 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 these conditions may be exacerbated.

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.

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 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. Aceclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Impaired Female 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.

Hypersensitivity Reactions: As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

Haematological: Aceclofenac may reversibly inhibit platelet aggregation.

Long-term Treatment
All patients who are receiving NSAIDs should be monitored as a precautionary measure e.g. renal failure, hepatic function (elevation of liver enzymes may occur) and blood counts.

Paracetamol

Hepatotoxicity: Paracetamol has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of paracetamol at doses that exceed 4,000 milligrams per day, and often involve more than one paracetamol containing product. The excessive intake of paracetamol may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other paracetamol-containing products.
The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking paracetamol.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Aceclofenac

Gastrointestinal: The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, 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 reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Cardiovascular and Cerebrovascular: Oedema, hypertension 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 (for example myocardial infarction or stroke).

The majority of adverse reactions reported have been reversible and of a minor nature. The most frequent are gastro-intestinal disorders, in particular dyspepsia, abdominal pain, nausea and diarrhoea, and occasional occurrence of dizziness. Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Dermatological complaints including pruritus and rash.

Investigations: Abnormal hepatic enzyme and serum creatinine levels have also been reported.

Other adverse reactions reported less commonly include:

Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

Hepatic: abnormal liver function, hepatitis and jaundice.

Neurological and special senses: Visual disturbances, optic neuritis, headaches, paraesthesia, 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, depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness.

Haematological: Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

Dermatological: Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare). Photosensitivity.

Paracetamol

Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia purpura, methaemoglobenaemia and agranulocytosis, but these were not necessarily causality related to paracetamol.

Thiocolchicoside

Thiocolchicoside can cause GI side effects such as nausea, vomiting, gastralgia, diarrhea and also CNS reaction such as anxiety, somnolence and rarely insomnia. As compared to tizanidine, thiocolchicoside is relatively devoid of drowsiness as a side effect.

Although rarely, decrease in blood pressure, temporary loss of consciousness (blurred conscious) or excitation can occur due to thiocolchicoside. During thiocolchicoside therapy, rash can develop in hypersensitive patients. Another concern of thiocolchicoside is the epileptogenic potential.

DRUG INTERACTIONS

Overview

Aceclofenac

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects.
Anti-hypertensives: Reduced anti-hypertensive effect.

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. 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.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR (glomerular filtration rate) and increase plasma glycoside levels.

Lithium: Decreased elimination of lithium

Methotrexate: Decreased elimination of 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.

Ciclosporin: Increased risk of nephrotoxicity.

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

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.

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

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Antidiabetic agents: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents with 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.

Anti-Coagulants: NSAIDs and Paracetamol may enhance the effects of anti-coagulants, such as warfarin. Close monitoring of patients on combined anti-coagulants and therapy should be undertaken.

Other NSAIDs: Concomitant therapy with aspirin or other NSAIDs may increase the frequency of adverse reactions, including the risk of GI bleeding.

Paracetamol

Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, the 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.

Chloramphenicol: Increased plasma concentration of chloramphenicol

DOSAGE AND ADMINISTRATION

Dosing Considerations

The recommended dose of Willgo – P is one tablet in morning and one tablet in evening preferably with or after food for the management of acute painful condition in adults.

USE IN SPECIAL POPULATION

Geriatric Use

The elderly, who are more likely to be suffering from impaired renal, cardiovascular or hepatic function and receiving concomitant medication, are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

Renal insufficiency

There is no evidence that the dosage of aceclofenac needs to be modified in patients with mild renal impairment, but as with other NSAIDs caution should be exercised.

Hepatic insufficiency

There is some evidence that the dose of aceclofenac should be reduced in patients with hepatic impairment and it is suggested that an initial daily dose of 100 mg be used.

Pregnancy

Willgo – P is a fixed combination of active ingredients including aceclofenac; it should not be used during pregnancy.

Aceclofenac: Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus) and on the possible risk of persistent pulmonary hypertension of the new born, use in the last trimester of pregnancy is contraindicated. The regular use of NSAIDs during the last trimester of pregnancy may decrease uterine tone and contraction. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and

child. NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Paracetamol: Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosages.

Lactation

Willgo – P is a fixed combination of active ingredients including aceclofenac; it should not be ingested during breast feeding.

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

Paracetamol : Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding by women using single ingredient medicinal products containing only paracetamol

OVERDOSAGE

Willgo – P is a combination product. The clinical presentation of overdose may include the signs and symptoms of aceclofenac toxicity, paracetamol toxicity or both.

Aceclofenac

a) Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal irritation, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, hypotension, respiratory depression, fainting, occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

b) Therapeutic measure

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose. Specific therapies such as dialysis or haemoperfusion are probable of no help in

eliminating NSAIDs due to their high rate of protein binding and extensive metabolism. Good urine output should be ensured. Renal and liver function should be closely monitored. Patients should be observed for at least four hours after ingestion of potentially toxic amounts. In case of frequent or prolonged convulsions, patients should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition. Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures

Paracetamol

The initial symptoms seen within the first 24 hours following an paracetamol overdose are: anorexia, nausea, vomiting, malaise, pallor and diaphoresis. In paracetamol over dosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and coagulation defects also may occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours postingestion.

In the treatment of paracetamol over dosage, gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if paracetamol ingestion is known or suspected to have occurred within a few hours of presentation. Serum paracetamol levels should be obtained immediately if the patient presents 4 or more hours after ingestion to assess potential risk of hepatotoxicity;
paracetamol levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration. Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose-dependent and occurs early in the course of intoxication.

Thiocolchicoside

There have been no reports on overdose with thiocolchicoside until now. In case of overdose, symptomatic and supportive therapy should be employed.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PHARMACODYNAMIC PROPERTIES

Aceclofenac

Aceclofenac is a non-steroidal agent with marked anti-inflammatory and analgesic properties. The mode of action of aceclofenac is largely based on the inhibition to prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo-oxygenase, which is involved in the production of prostaglandins.

Paracetamol

Analgesic the mechanism of analgesic action 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 pain-impulse generation. The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

Thiocolchicoside

Thiocolchicoside is a centrally acting skeletal muscle relaxant with additional anti-inflammatory, analgesic actions. Thiocolchicoside interacts with Gamma Aminobutyric acid GABA type A receptors (GABAARs) and strychnine- sensitive glycine receptors in the central nervous system (CNS) basically in the brainstem and spinal cord.

PHARMACOKINETICS 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 L.

The mean plasma elimination half-life is around 4 hours. Aceclofenac is highly protein- bound (>99%). Aceclofenac circulates mainly as unchanged drug. 4'-Hydroxyaceclofenac is the main metabolite detected in plasma. 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

Absorption and Fate
Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolised 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.

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9L/kg. A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

Thiocolchicoside

Absorption and Blood Levels
Thiocolchicoside is rapidly absorbed and peak concentration are achieved in 0.4 hour.Bioavailability is low since it has extensive first pass metabolism. Its terminal half life is 0.5 hours

Fate
De-glycosylation of thiocolchicoside produces the aglycone derivative (M1 metabolite); this is in addition to the main active metabolite (M1) i.e. 3-O-glucoronidated aglycone. M1 + M2 metabolites account for 75% of the circulating thiocolchicoside. M1 metabolite appears in 1 hour and has a terminal elimination half-life of 7.3 hours.

STORAGE AND STABILITY

Store at a temperature not more than 30°C, protected from light and moisture.
Keep the medicine out of reach of children.

SPECIAL HANDLING INSTRUCTIONS

No special requirements.

DOSAGE FORMS: Tablets Oral Administration

SHELF LIFE

24 months

PACKAGING INFORMATION

Blister Pack of 10x10s tablets.

COMPOSITION:

RF Willgo

Each film coated tablet contains:

Aceclofenac IP	100 mg
Paracetamol IP	325 mg

Colours: Ferric Oxide (Yellow) and Titanium Dioxide

Willgo TH

Each capsule contains

Aceclofenac IP (As sustained – release form)	200 mg
Thiocolchicoside (As sustained – release form)	8 mg

PHARMACEUTICAL INFORMATION

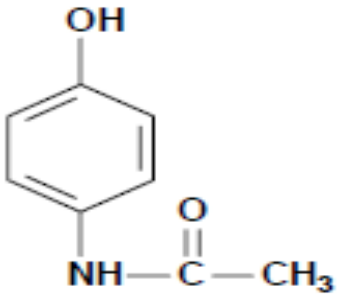
Drug Substance

Proper name: Acetaminophen

Chemical name: Acetamide, N-(4 – hydroxyphenyl)- 4 – Hydroxyacetanilide

Molecular formula and molecular mass: 151.16

Structural formula:



Physicochemical properties:

Description:	White crystalline powder (Verschueren, 1996)
Melting-point:	170°C (Lide, 1997)
Density:	1.293 g/cm3 at 21°C (Lide, 1997)
Solubility:	Insoluble in water; very soluble in ethanol (Lide, 1997)
Octanol/water partition coefficient (P):	log P, 0.31 (Hansch et al., 1995)
Conversion factor: mg/m3 =	6.18 × ppm

Drug Substance

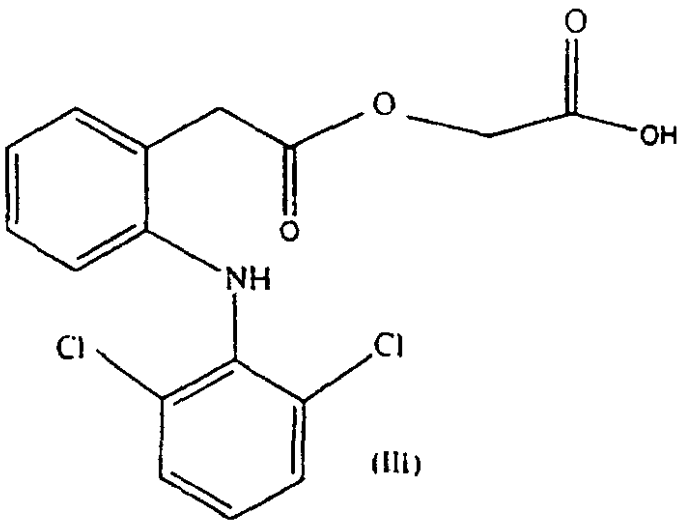
Proper name: Aceclofenac

Chemical name: 2-[2-[2-(2,6-dichloroanilino)phenyl]acetyl]oxyacetic acid

Molecular formula: $C_{16}\ H_{13}\ Cl_2\ N\ O_4$

Molecular mass: 354.18

Structural formula:



(III)

Drug Substance

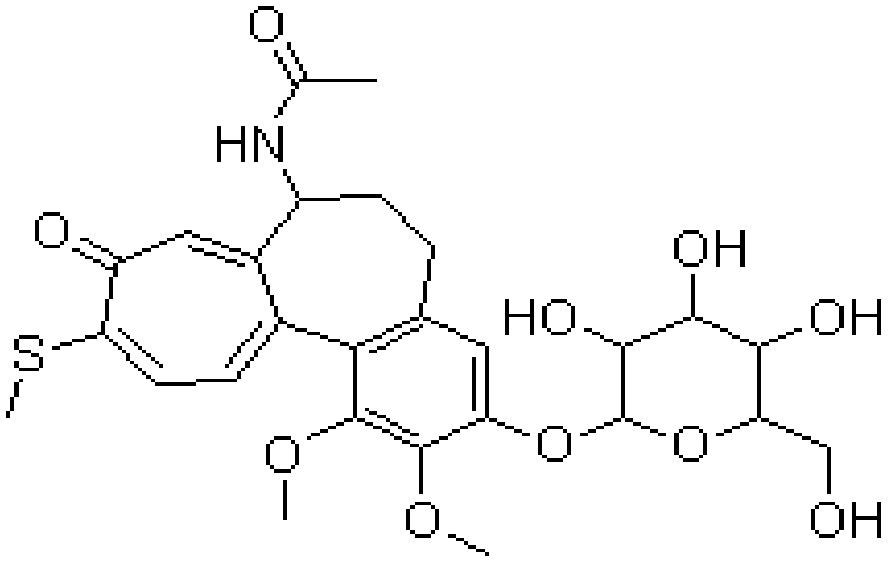
Proper name: Thiocolchicoside

Chemical name: 2,14-di-(demethoxy)-2-glucosidoxy-14-methylthiocolchicine

Molecular formula: $C_{27}H_{33}NO_{10}S$

Molecular mass: 563.6 g/mol

Structural formula:



Remember, keep this and all other medicines out of the reach of children, never share your medicines with others, and use this medication only for the indication prescribed.

This product monograph, prepared for health professionals can be found at:

Panacea Biotec Web site www.panaceabiotec.com

or by contacting the Panacea Biotec Limited (INDIA).

Address for correspondence:

Panacea Biotec Limited

B-1 Extn / G-3, Mohan Co-operative Industrial Estate,

Mathura Road, New Delhi – 110 044

Last revised: 20 August 2014