For the use of a Registered Medical Practitioner only

CARDIOVASCULAR RISK

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
- Diclofenac sodium is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery

GASTROINTESTINAL RISK

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

1. GENERIC NAME AND BRAND NAME

Eperisone Hydrochloride Sustained Release 150mg & Diclofenac Sodium Sustained Release 100mg Capsules

RAPISONE-D SR®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains:
Eperisone Hydrochloride JP 150mg (as sustained release pellets)
Diclofenac Sodium I.P. 100mg (as sustained release tablet)
Excipients q.s
Colour: Ferric oxide USP-NF (Yellow)
Approved colours used in capsule shell:
Tartrazine, Sunset Yellow FCF & Titanium Dioxide I.P.

3. DOSAGE AND STRENGTH

Refer section 1 & 2

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATION

For the treatment of patient with acute musculoskeletal spasm associated with low back pain.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

One capsule per day after meals

4.3 CONTRAINDICATIONS

- Known hypersensitivity to Eperisone or Diclofenac
- Diclofenac should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.
- Diclofenac is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Eperisone

Careful Administration

(1) Patients with a history of drug hypersensitivity

(2) Patients with hepatic function disorder

Important Precautions

Weakness, sleepiness, light-headedness or other symptoms may occur during treatment with Eperisone. In the event of such symptoms, the dosage should be reduced or treatment discontinued. Patients should be cautioned against engaging in potentially hazardous activities requiring alertness, such as driving a car or operating machinery.

Use in the Elderly

Since the elderly often have reduced physiological functions, it is suggested to exercise careful supervision and take measures such as reducing the dosage.

Use during Pregnancy, Delivery or Lactation

(1) Eperisone should be used in pregnant women or women suspected of being pregnant, only if the expected therapeutic benefits are evaluated to outweigh the possible risks of treatment.

(2) It is suggested to avoid administration of Eperisone to nursing mothers.

Pediatric Use

Safety in children has not been established.

Diclofenac

Cardiovascular Effects

- **Cardiovascular Thrombotic Events**

Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with diclofenac, the lowest effective dose should be used for the shortest duration possible.

- **Hypertension**

NSAIDs can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

- **Congestive Heart Failure and Edema**

Fluid retention and oedema have been seen in some patients taking NSAIDs. Diclofenac should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal (GI) Effects: Risk of GI Ulceration, Bleeding, and Perforation

NSAIDs, including Diclofenac, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal.For high risk patients, alternate therapies that do not involve diclofenac should be considered.

Renal Effects

Caution should be used when initiating treatment with Diclofenac in patients with considerable dehydration. Renal toxicity has been observed in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion.

Advanced Renal Disease

Treatment with Diclofenac is not recommended in these patients with advanced renal disease.

Hepatic Effects

Caution should be exercised in prescribing Diclofenac with concomitant drugs that are known to be potentially hepatotoxic (e.g., antibiotics, anti-epileptics).

Anaphylactic Reactions

Diclofenac should not be given to patients with the aspirin triad. As with other NSAIDs, anaphylactic reactions may occur both in patients with the aspirin triad and in patients without known sensitivity to NSAIDs or known prior exposure to Diclofenac.

Skin Reactions

NSAIDs, including Diclofenac, can cause serious skin adverse events such as exfoliativeStevens-Johnson Syndrome (SJS), dermatitis and toxic epidermal necrolysis (TEN), which can be fatal.

The drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

In late pregnancy, Diclofenac should be avoided as it may cause premature closure of the ductusarteriosus.

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs, including Diclofenac. Patients receiving Diclofenac who may be adversely affected by alterations in platelet function.

Preexisting Asthma

Diclofenac should not be administered to patients with aspirin sensitivity and should be used with caution in all patients with preexisting asthma.

4.5 DRUG INTERACTIONS

Drug	Drug Interaction	Remark
Methocarbamol	It has been reported that disturbance of visual accommodation occurred after concomitant use of methocarbamol	Mechanism unknown

	with tolperizone hydrochloride, an analogous compound.	
Aspirin	When Diclofenac is administered with aspirin, its protein binding is reduced.	The clinical significance of this interaction is not known.
Methotrexate	NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices.	Caution should be used when NSAIDs are administered concomitantly with methotrexate.
Cyclosporine	Concomitant therapy with Diclofenac may increase cyclosporine's nephrotoxicity.	Caution should be used when Diclofenac is administered concomitantly with cyclosporine.
ACE Inhibitors	NSAIDs may diminish the antihypertensive effect of ACE inhibitors.	-
Furosemide	Diclofenac can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.	During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.
Lithium	NSAIDs produce an elevation of plasma lithium levels and a reduction in renal lithium clearance.	NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.
Warfarin	The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.	-
CYP2C9 Inhibitors or Inducers	Co-administration of diclofenac with CYP2C9 inhibitors (e.g. voriconazole) may enhance the exposure and toxicity of diclofenac whereas co-administration with CYP2C9 inducers (e.g. rifampin) may lead to compromised efficacy of diclofenac.	-

4.6 USE IN SPECIAL POPULATION (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Use During Pregnancy:

Eperisone hydrochloride should only be used in pregnant women or women suspected of being pregnant, if the expected therapeutic benefits are evaluated to outweigh the possible risk of treatment.
[The safety of Eperisone hydrochloride in pregnant women has not been established.]

Use of NSAIDs, including Diclofenac, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including Diclofenac, in pregnant women starting at 30 weeks of gestation (third trimester). There are no adequate and well-controlled studies of Diclofenac in pregnant women. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decasualization. In animal studies, administration of prostaglandin synthesis inhibitors such as Diclofenac, resulted in increased pre- and post-implantation loss.

There are no studies on the effects of Diclofenac during labor or delivery. In animal studies, NSAIDS, including Diclofenac, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Use During Lactation:

It is advisable to avoid the administration of Eperisone hydrochloride to nursing mothers. When Eperisone hydrochloride must be used, breast feeding should be discontinued during treatment. [It has been reported that Eperisone hydrochloride is excreted in breast milk in an animal study (in rats).]

Based on available data, Diclofenac may be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Diclofenac and any potential adverse effects on the breastfed infant from the Diclofenac or from the underlying maternal condition.

Caution should be exercised when acetaminophen is administered to a nursing woman

Pediatric

There is no data regarding use of Eperisone hydrochloride in children.

Diclofenac Tablets are not recommended for children under 14 years of age.The use of diclofenac tablets in migraine attacks has not been established in children.

Geriatric patients

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated

benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no data regarding the effects of Eperisone hydrochloride on driving or operating machinery. Until the effects of Eperisone hydrochloride are known, patients should be advised to avoid driving or operating machinery since Eperisone hydrochloride can cause sleepiness.

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

Caution is also suggested in
- Patients taking diuretics and elderly
- Excess dosage should be avoided.

4.8 UNDESIRABLE EFFECTS

Eperisone

Clinically significant adverse reactions

Shock and anaphylactoid reactions

Since shock and anaphylactoid reactions may occur, patients should be carefully observed. In the event of symptoms such as redness, urticaria, itching, edema of the face or other parts and dyspnea etc., treatment should be discontinued, and appropriate measures should be taken.

Toxic epidermal necrolysis (TEN) and Oculomucocutaneous syndrome (Stevens-Johnson syndrome)

Because Eperisone may cause serious skin disorders including Toxic Epidermal Necrolysis (TEN) and oculomucocutaneous syndrome etc., patients receiving this medication should be carefully monitored for symptoms such as erythema, blisters, itchiness, fever, ocular hyperemia, and stomatitis. If any of these symptoms appear, administration should be discontinued, and appropriate measures should be taken.

Other adverse reactions

	<0.1%	**0.1%-5%**	**Incidence unknown**
Hepatic	Elevations of AST (GOT), ALT (GPT) and AI-P, etc.		
Renal	Proteinuria and Elevation of BUN, etc.		
Hematologic [note 1]	Anemia		
Hypersensitivity [note 2]	Pruritus	Rash	Erythema exudativummultiforme
Psychoneurologic	Stiffness and temor in the extremities	Sleepiness, insomnia, headache	

		and numbness in the extremities	
Gastrointestinal	Stomatitis and feeling of enlarged abdomen	Nausea/vomiting, anorexia, stomach discomfort, abdominal pain, diarrhea, constipation and thirst	
Urinary	Urinary retention, urinary incontinence and feeling of residual urine		
General	Muscle hypotonia and dizziness	Weakness, light-headedness and generalized fatigue	
Others	Diaphoresis and edema	Hot flushes	

Diclofenac

In patients taking diclofenac or other NSAIDs, the most frequently reported adverse experiences occurring in approximately 1%-10% of patients are:

Gastrointestinal experiences including: constipation, diarrhoea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, abdominal pain, nausea, GI ulcers (gastric/duodenal) and vomiting.

Abnormal renal function, dizziness, edema, elevated liver enzymes, anemia, headaches, pruritus, rashes, increased bleeding time and tinnitus.

Additional adverse experiences reported occasionally include:

Body as a Whole: infection, sepsis, fever

Cardiovascular System: hypertension, tachycardia, syncope, congestive heart failure

Hemic and Lymphatic System: eosinophilia, melena, purpura, rectal bleeding, stomatitis, thrombocytopenia, ecchymosis, leukopenia

Metabolic and Nutritional: weight changes

Digestive System: esophagitis, gastric/peptic ulcers, dry mouth, gastritis, gastrointestinal bleeding, hematemesis, hepatitis, jaundice, glossitis

Nervous System: asthenia, depression, dream abnormalities, drowsiness, insomnia, malaise, nervousness, paresthesia, anxiety, somnolence, tremors, vertigo, confusion

Respiratory System: dyspne, asthma, Skin and Appendages: alopecia, photosensitivity, sweating increased Special Senses: blurred vision.

Urogenital System: dysuria, interstitial nephritis, cystitis, oliguria/polyuria, hematuria, proteinuria, renal failure.

Other adverse reactions, which occur rarely are:

Body as a Whole: appetite changes, anaphylactic reactions, death

Hemic and Lymphatic System: hemolyticanemia, aplastic anemia, agranulocytosis, lymphadenopathy, pancytopenia
Metabolic and Nutritional: hyperglycemia
Digestive System: eructation, fulminant hepatitis with and without jaundice, colitis, liver failure, pancreatitis, liver necrosis
Nervous System: convulsions, hallucinations, meningitis, coma
Respiratory System: pneumonia, respiratory depression
Skin and Appendages: toxic epidermal necrolysis, angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria
Cardiovascular System: hypotension, myocardial infarction, arrhythmia, palpitations, vasculitis
Special Senses: hearing impairment, conjunctivitis

4.9 OVERDOSE

Seizures have been reported in an infant after accidental ingestion of eperisone.
NSAID overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are also possible.

Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.
Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion of a potentially toxic overdose.
Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1 MECHANISM OF ACTION

Eperisone hydrochloride is a centrally acting muscle relaxant acting through poly and mono-synaptic reflexes in the spinal cord, exhibits vasodilator effect, increases blood flow and inhibits the pain reflex pathway. This helps in reducing the intensity of pain with eperisone and possibly contributes to its analgesic activity. Eperisone hydrochloride acts by depressing the activities of α and γ efferent neurons in the spinal cord and supraspinal structures. Its action mechanism involves inhibition of neural activity and pain sensation by blocking the voltage-gated sodium channels (VGSC) in the brain stem.

Diclofenac sodium is a non-steroidal compound with pronounced and clinically demonstrable analgesic, anti-inflammatory and anti-pyretic properties.

Diclofenac is a potent inhibitor of prostaglandin biosynthesis and a modulator of arachidonic acid release and uptake.

Diclofenac sodium tablets have a rapid onset of action and are therefore suitable for the treatment of acute episodes of pain and inflammation.

In migraine attacks Diclofenac sodium tablets have been shown to be effective in relieving the headache and in improving the accompanying symptom of nausea.

Diclofenac *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

5.2 PHARMACODYNAMIC PROPERTIES

1. Skeletal muscle relaxation
    - Inhibition of experimentally induced muscle rigidity: Eperisone hydrochloride suppresses intercollicular section-induced decerebrate rigidity (y-rigidity) and ischemic decerebrate rigidity (a-rigidity) in rats dose-dependently.
    - Suppression of spinal reflexes: In spinal cats, eperisone hydrochloride suppresses mono and poly-synaptic reflex potentials induced through spinal nerve efferent root stimulation to a similar degree.
    - Reduction of muscle spindle sensitivity via y-motor neurons: Eperisone hydrochloride suppresses the activity of afferent nerve fibers (la fibers) from human muscle spindles at 20 min after administration. Eperisone hydrochloride suppresses the spontaneous discharge of γ-motor neurons but does not act directly on muscle spindles in animals. Accordingly, eperisone hydrochloride reduces muscle spindle sensitivity viathe γ-motor neurons.
    - Vasodilatation and augmentation of blood flow:
    - Vasodilatory action: Eperisone hydrochloride dilates the blood vessels due to Ca** antagonistic action (in guinea pigs) on the vascular smooth muscle and muscular sympatholytic actions (in humans).
    - Augmentation of blood flow: Eperisone hydrochloride increases the volume of blood flow in skin, muscle, external and internal carotid arteries and vertebral arteries in humans, monkeys and dogs.
    - Analgesic action and inhibition of the pain reflex in the spinal cord:
      When eperisone hydrochloride is perfused into the spinal cord of rats, a tail pinch-induced pain reflex is suppressed, but the reflex returns with th withdrawal of eperisone hydrochloride. This suggests that eperisone hydrochloride possesses an analgesic action at the spinal cord level.
    - Facilitation of voluntary movement:
      When eperisone hydrochloride is used in the treatment of spastic paralysis in patients with cerebral apoplexy, it improves the cybex torque curve and electromyogram and facilitates voluntary movements, such as extension and flexion of the extremities, without reducing the muscular force.
    - Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action is not completely understood but may be related to prostaglandin synthetase inhibition.

5.3 PHARMACOKIETIC PROPERTIES

	Eperisone HCl	**Diclofenac Sodium**
Absorption	Well absorbed orally	Diclofenac is 100% absorbed after oral administration.

Distribution	-	The apparent volume of distribution (V/F) of diclofenac sodium is 1.4 L/kg. Diclofenac is more than 99% bound to human serum proteins, primarily to albumin.
Metabolism	-	Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'- hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy- diclofenac.
Elimination	$T_{1/2}$ = 1.6 - 1.8 hour	Approximately 65% of the dose is excreted in the urine and approximately 35% in the bile as conjugates of unchanged diclofenac plus metabolites.

6. NONCLINICAL PROPERTIES
6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

Effects of eperisone, an antispasmodic in skeletal muscle, were investigated in helical strips of dog saphenous artery and vein. Eperisone relaxed saphenous arteries and veins previously contracted with norepinephrine, serotonin, acetylcholine, K+, or Ba2+. eperisone blocks postjunctional alpha 1- and alpha 2-adrenergic, muscarinic, serotonergic receptors and prejunctional alpha 2 adrenoceptors and reduces PGI2 synthesis via a mechanism other tha

Eperisone, a Ca2+ entry blocker, suppressed the action of tumor promoter in vitro and in vivo, inhibited tumor-promoter-stimulated 32Pi incorporation into phospholipids of cultured cells, and also proved to have antitumor-promoting activity in mouse skin carcinogenesis induced by 7,12- dimethylbenz[a]anthracene plus tumor promoter, 12-O-tetradecanoylphorbol-13-acetate.

Reproductive and developmental studies in animals demonstrated that Diclofenac sodium administration during organogenesis did not produce teratogenicity despite the induction of maternal toxicity and fetal toxicity in mice at oral doses up to 20 mg/kg/day (approximately 0.5 times the maximum recommended human dose [MRHD] of Diclofenac, 200 mg/day, based on body surface area (BSA) comparison), and in rats and rabbits at oral doses up to 10 mg/kg/day (approximately 0.5 and 1 times, respectively, the MRHD based on BSA comparison). Diclofenac has been shown to cross the placental barrier in mice, rats, and humans.

7. DESCRIPTION
RAPISONE-D SR is supplied for oral administration, as a sustained release capsule of Eperisone Hydrochloride & Diclofenac Sodium. Each hard gelatin capsule of RAPISONE-D SR contains Eperisone Hydrochloride 150mg (as sustained release pellets) & Diclofenac Sodium 100mg (as sustained release tablet).

8. PHARMACEUTICAL PARTICULARS
8.1 INCOMPATIBILITIES
Not applicable

8.2 SHELF-LIFE
Refer pack

8.3 PACKAGING INFORMATION
Refer pack

8.4 STORAGE CONDITION AND HANDLING INSTRUCTIONS
Refer pack

9. PATIENT COUNSELLING INFORMATION

Advise the patients to inform the doctor before taking this medicine if

- They have previously experienced any allergic reactions(itch,rach,etc.) to any medicines.
- They have hepatic disorder.
- They are pregnant or breastfeeding.
- They are taking any other medicinal products. (Some medicines may interact to enhance or diminish medicinal effects. Beware of over-the-counter medicines and dietary supplements as well as other prescription medicines.)

This medicine also contains diclofenac

Advise the patients to tell their doctor about all their your medical conditions, including if they:

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Patients must talk to their doctor if they are considering taking NSAIDs during pregnancy.

Patients must take this tablet:

- exactly as prescribed
- at the lowest dose possible for the treatment
- for the shortest time needed

Patients must not take this tablet

- if they have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Patients must tell your healthcare provider about all of the medicines they take, including prescription or over-the-counter medicines, vitamins, or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. Patients must not start taking any new medicine without talking to their doctor first**.**

Patients must stop taking the NSAID and call the doctor immediately if they get any of the following symptoms

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in stools or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

10. DETAILS OF MANUFACTURER
Refer Pack for manufacturer details.

Marketed By:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 6 &
11 to 16 Ground Floor, 101 to 106 &
111 to 116 First Floor, 201 to 206 & 211 to 216
2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER
Refer Pack for Permission/License details

12. DATE OF REVISION
Version 4.0 dated 21st Sept 2023

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For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com