For the use of a Registered Medical Practitioners or a Hospital or a Laboratory only

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TEXXA - D

(Tolperisone Hydrochloride Sustained Release 450 mg and Diclofenac Sodium Sustained Release 100 mg Tablets)

COMPOSITION

Each uncoated bilayered sustained release tablet contains:

Tolperisone Hydrochloride J.P. …….450 mg

Diclofenac Sodium I.P. ……100 mg

Excipients……..q.s.

Colour: Ferric Oxide USP-NF (Yellow)

INDICATION

For the treatment of Patients with acute muscle/musculo skeletal spasm in adult.

POSOLOGY AND METHOD OF ADMINISTRATION

It is recommended that Texxa – D should be administered under the supervision of physicians. Tablet should be taken as a whole with water without crushing or chewing.

Tolperisone

Posology

Tolperisone should be used as prescribed by the physician. General recommendations are:

Adults and adolescents from age 15: daily dose is 150 mg – 450 mg per os divided into 3 doses, according to the individual requirements and tolerance of the patients. This dosage can also be applied for long-term treatment (several months or years) without dose reduction. In the elderly dose modification or reduction is not necessary; the doses recommended are well tolerated.

Paediatric population:

The safety and efficacy of tolperisone in children have not been established.

Patients with renal impairment:

Experience in patients with renal impairment is limited and a higher frequency of adverse events has been observed in this patient group. Therefore, individual titration with close monitoring of the patient's condition and renal function is recommended in patients with moderate renal impairment. Use of tolperisone is not recommended in patients with severe renal impairment.

Patients with hepatic impairment:

Experience in patients with hepatic impairment is limited and a higher frequency of adverse events has been observed in this patient group. Therefore, individual titration with close monitoring of the patient's condition and hepatic function is recommended in patients with moderate hepatic impairment. Use of tolperisone is not recommended in patients with severe hepatic impairment.

Method of administration:

The medicine should be taken after meals with a glass of water.

Insufficient food intake may decrease the bioavailability of tolperisone.

Diclofenac Sodium

As a general recommendation, the dose should be individually adjusted and the lowest effective dose given for the shortest possible duration. The tablets should be swallowed whole with liquid, preferably with meals and must not be divided or chewed.

Adults

The recommended initial daily dose is 100 to 150 mg, administered as 1 tablet of Diclofenac Sodium 100 mg. In milder cases, as well as for long-term therapy, 100 mg daily is usually sufficient. Where the symptoms are most pronounced during the night or in the morning, Diclofenac Sodium 100 mg should preferably be taken in the evening.

Children and adolescents

Because of their dosage strength, Diclofenac Sodium 100 mg are not suitable for children and adolescents.

CONTRAINDICATIONS

Tolperisone

- Hypersensitivity to the active substance tolperisone or to the chemically similar eperisone or to any of the excipients.
- Myasthenia gravis.
- Lactation.

Diclofenac Sodium

- Known hypersensitivity to the active substance or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation.
- Last trimester of pregnancy
- Severe hepatic, renal or cardiac failure
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac sodium is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Tolperisone

Special attention is required in treatment of patients who already receiving antihypertensive therapy, since according preliminary clinical observations tolperisone may cause decreased blood pressure of approximately 10 to 30 mm Hg in transient after a single dose or in case of long-term therapy as well.

There is no need of reduction or modification of dosages in special treatment groups such as elderly people, however as it is known that inter-individual variations may require attention and the oral doses of tolperisone might need to be individualized.

Inter-individual differences may be observed in all treatment groups, based on the metabolism, which takes place primarily in the liver. Tolperisone undergoes an extensive first pass effect, and only 20% of an administered dose appear unchanged in the blood. The metabolism is NADPH-dependent, since the omission of this coenzyme completely abolished the consumption of tolperisone. It has been demonstrated that both P450- dependent and P450-independent microsomal biotransformations are involved in tolperisone metabolism, in vitro. Hydroxymethyl metabolite formation revealed to be the main P450-mediated metabolic pathway. CYP2D6 was identified as the key enzyme in metabolism, however involvement of CYP2C19 and CYP1A2 were also shown in lesser extent. It was evidenced that P450 independent metabolism was mediated to a small extent by FMO3. Metabolites detected and indirect evidences from inhibition studies pointed toward the substantial involvement of presumable microsomal carbonyl reductase in the metabolism of tolperisone.

Hypersensitivity reactions

During post marketing experience with tolperisone the most frequently reported adverse reactions were hypersensitivity reactions. Hypersensitivity reactions ranged from mild skin reactions to severe systemic reactions including anaphylactic shock. Symptoms may include erythema, rash, urticaria, pruritus, angioedema, tachycardia, hypotension or dyspnoea. Females, patients with hypersensitivity to other drugs or with a history of allergy may be at a higher risk. In case of a known hypersensitivity to lidocaine increased caution during the administration of tolperisone because of possible cross-reactions is warranted. Patients should be advised to remain vigilant for any symptoms compatible with hypersensitivity and to stop tolperisone and seek medical advice immediately if such symptoms occur. Tolperisone must not be readministered after an episode of hypersensitivity to tolperisone.

Diclofenac Sodium

Precaution:

Severe cutaneous reactions, including Stevens - Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), have been reported with diclofenac sodium. Patients treated with diclofenac sodium should be closely monitored for signs of hypersensitivity reactions. Discontinue diclofenac sodium immediately if rash occurs.

Warning:

Risk of GI ulceration, bleeding and perforation with NSAID

Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in theraphy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug.

Like other NSAIDs, diclofenac sodium may mask the signs and symptoms of infection due to its pharmacodynamic properties.

The concomitant use of diclofenac sodium with systemic NSAIDs including cyclooxygenase 2 selective inhibitors, should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.

Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

Pre-existing asthma

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

Gastrointestinal effects

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low-dose acetylsalicylic acid (ASA)/aspirin or other medicinal products likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors.

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated.

Hepatic effects

Close medical surveillance is required when prescribing diclofenac sodium to patients with impaired hepatic function, as their condition may be exacerbated.

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac sodium, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), diclofenac sodium should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

Caution is called for when using diclofenac sodium in patients with hepatic porphyria, since it may trigger an attack.

Renal effects

As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery. Monitoring of renal function is recommended as a precautionary measure when using diclofenac sodium in such cases. Discontinuation of therapy is usually followed by recovery to the pretreatment state.

Haematological effects

During prolonged treatment with diclofenac sodium, as with other NSAIDs, monitoring of the blood count is recommended. Like other NSAIDs, diclofenac sodium may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

DRUG-INTERACTION

Tolperisone

No interaction between tolperisone and medications prescribed for concomitant diseases has been observed that would restrict the administration of tolperisone. However, tolperisone is metabolised by the cytochrome P450 system, in particular CYP2D6. Therefore, interactions with drugs that are metabolised by the same system cannot be excluded. Tolperisone does not affect cortical functions and the arousal level; therefore, it can be given together with hypnotics, sedatives and tranquillizers. However, dose reduction may be considered when tolperisone tablets are administered concomitantly with other centrally acting muscle relaxants. On the basis of clinical trials, it can be concluded that tolperisone potentiates the effect of NSAIDs.

Additional that has described in 4.4, in treatment of patients who already receiving antihypertensive therapy, possible interactions may be considered, however there is no direct evidences of clinical observations reported. Based on the current data tolperisone inhibits reflexes by two main mechanisms: on the one hand by influencing the inhibition of voltage-dependent sodium channels, and on the other hand by influencing synaptic transmission through inhibiting sodium and calcium channels. However, additional mechanisms can not be completely excluded (e. g. effects through alpha receptors). A theoretical sites of interference can not be ruled out due the direct inhibition of tolperisone, on the Na2+ and in lesser extent on the Ca2+ channels in experimental conditions. However, reports showed that the Ca2+ antagonistic action occurring generally in higher concentrations, compared to the action on Na2+ channels. The sites and extent of possible interactions need to be elucidated.

Tolperisone tablets do not cause either somatic or psychical dependency. According to present data tolperisone tablets do not have any influence on the results of clinical laboratory examinations.

Pharmacokinetic drug interaction studies with the CYP2D6 substrate dextromethorphan indicate that tolperisone co-administration may increase the blood levels of drugs which are metabolised dominantly by CYP2D6 such as thioridazine, tolterodine, venlafaxine, atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine. In vitro experiments in human liver microsomes and human hepatocytes did not suggest significant

inhibition or induction of other CYP isoenzymes (CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP1A2, CYP3A4). Increase in tolperisone exposure is not expected after concomitant administration of CYP2D6 substrates and/or other drugs due to the diversity of the metabolic pathways of tolperisone. The bioavailability of tolperisone is decreased when taken without food, therefore consistent administration in relation to meals is recommended. Although tolperisone is a centrally acting compound, its potential to cause sedation is low. In the case of co-administration with other centrally acting muscle relaxants, the dose reduction of tolperisone should be considered. Tolperisone potentiates the effect of niflumic acid, therefore reduction of the dose of niflumic acid or other NSAID should be considered in case of coadministration.

Diclofenac Sodium

The following interactions include those observed with diclofenac sodium enteric-coated tablets and/or other pharmaceutical forms of diclofenac.

Lithium

If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin

If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive agents

Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently.

Other NSAIDs and corticosteroids

Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects.

Anticoagulants and anti-platelet agents

Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are isolated reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs)

Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding.

Antidiabetics

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 both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate

Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

Ciclosporin

Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Quinolone antibacterials

There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

FERTILITY, PREGNANCY AND LACTATION

Tolperisone

Pregnancy

No teratogenic effect of tolperisone was noted in any animal studies. Since there are no human study results available, tolperisone should only be used in pregnancy (especially in the first trimester), if the expected therapeutic benefits are unambiguously higher than the foetal risk.

Lactation

Since there are no data available whether tolperisone is excreted into breast milk, it must not be used during lactation.

Diclofenac Sodium

Pregnancy

The use of diclofenac in pregnant women has not been studied. Therefore, diclofenac sodium should not be used during the first two trimesters of pregnancy unless the potential benefit to the mother outweighs the risk to the foetus. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus. Animal studies have not shown any directly or indirectly harmful effects on pregnancy, embryonal/foetal development, parturition or postnatal development.

Lactation

Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, diclofenac sodium should not be administered during breast feeding in order to avoid

undesirable effects in the infant.

Fertility

As with other NSAIDs, the use of diclofenac sodium 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 diclofenac sodium should be considered.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tolperisone

No studies on the effects on the ability to drive and use machines have been performed. Patients who experience dizziness, somnolence, disturbance in attention, epilepsy, blurred vision or muscular weakness while taking tolperisone should consult his/her doctor

Diclofenac Sodium

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

UNDESIRABLE EFFECTS

Tolperisone

Undesirable effects of Tolperisone are transient, and decrease or even stop by reducing the dose.

Adverse events are listed below by frequency as follows. very common: ≥1/10, common ≥1/100 to <1/10, uncommon ≥1/1,000 to < 1/100, rare ≥1/10,000 to < 1/1,000, very rare < 1/10,000, not known: cannot be estimated from the available data.

The safety profile of tolperisone containing tablets is supported by data on more than 12,000 patients. According to these data, the most frequently concerned system organ classes are skin and subcutaneous tissue disorders, general disorders, neurological disorders and gastrointestinal disorders.

Nervous system disorders	
Uncommon	dizziness, sleepiness
Rare	headache, sleep disturbance
Gastrointestinal disorders	
Uncommon	abdominal discomfort, nausea, vomiting, dry mouth, abdominal pain
Rare	constipation, diarrhoea, gastrointestinal disturbance
Skin and subcutaneous tissue disorders	
Rare	increased sweating
Psychiatric disorders	
Uncommon	fatigue, lassitude, weakness
Immune system disorders	
Rare	hypersensitivity reaction with erythema, exanthema, pruritus, blood pressure decreased and increased heart rate

Very rare	hypersensitivity reaction with urticaria, dyspnoea, angioneurotic oedema in single cases, anaphylactic shock

In cases of any hypersensitivity reaction, the administration of tolperisone should be discontinued.

In post-marketing data, hypersensitivity reactions associated with tolperisone administration account for about 50-60% of the reported cases. The majority of the cases express non-serious and self-limiting conditions. Life-threatening hypersensitivity reactions are reported very rarely.

Diclofenac Sodium

Adverse effects:
Dermatological: Occasional - rashes or skin eruptions.
Cases of hair loss, bullous eruptions, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), and photosensitivity reactions have been reported.

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

The following undesirable effects include those reported with diclofenac sodium SR tablets and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Blood and lymphatic system disorders
Very rare: Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.
Immune system disorders
Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare: Angioneurotic oedema (including face oedema).

Psychiatric disorders
Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

Nervous system disorders
Common: Headache, dizziness.
Rare: Somnolence.
Very rare: Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.

Eye disorders
Very rare: Visual disturbance, vision blurred, diplopia.

Ear and labyrinth disorders
Common: Vertigo.
Very rare: Tinnitus, hearing impaired.

Cardiac disorders

Very rare: Palpitations, chest pain, cardiac failure, myocardial infarction.

Vascular disorders
Very rare: Hypertension, vasculitis.

Respiratory, thoracic and mediastinal disorders
Rare: Asthma (including dyspnoea).
Very rare: Pneumonitis.

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare: Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or perforation).
Very rare: Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.

Hepatobiliary disorders
Common: Transaminases increased.
Rare: Hepatitis, jaundice, liver disorder.
Very rare: Fulminant hepatitis, hepatic necrosis, hepatic failure

Skin and subcutaneous tissue disorders
Common: Rash.
Rare: Urticaria.
Very rare: Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.
Renal and urinary disorders
Very rare: Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.

General disorders and administration site conditions
Rare: Oedema.

OVERDOSE

Tolperisone

There are limited data available on the overdose of tolperisone. The therapeutic index of tolperisone is wide and there are literature reports of oral administration of 600mg tolperisone in children without any severe toxic symptom. In some children 300–600mg/day tolperisone administered orally was associated with irritability. Tolperisone has no specific antidote. In tolperisone overdose general symptomatic and supportive measures should be taken.

Diclofenac Sodium

Symptoms
There is no typical clinical picture resulting from diclofenac overdosage. 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 possible.

Therapeutic measures
Management of acute poisoning with NSAIDs, including diclofenac essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism. Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life threatening overdose.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Tolperisone

Pharmacotherapeutic group: other centrally acting agents

Tolperisone is a centrally acting muscle relaxant with properties similar to local anaesthetics. The precise mechanism of action of tolperisone is not fully known. It possesses high affinity for nervous tissue, reaching the highest concentration in the brain stem, spinal cord and peripheral nerve tissue. The chemical structure of tolperisone is similar to that of lidocaine and, similarly to lidocaine, tolperisone has membrane stabilising effects. Tolperisone reduces the sodium influx through the isolated nerve membrane in a dose dependent way, thus amplitude and frequency of action potentials are reduced. Furthermore, inhibitory effects on voltage dependent Ca2+ channels have been demonstrated, suggesting that tolperisone might also reduce the transmitter release in addition to its membrane stabilising effect.
Tolperisone exerts its action at 3 levels:

- Peripheral level - Tolperisone stabilises the cell membrane of neurons, and consequently suppresses the amplitude and frequency of the action potentials. It is capable of inhibiting the pathological peripheral impulse condition induced by pain, which could start various motoric or vegetative reflexes that would lead to increased muscular tone.
- Central-spinal level - Tolperisone reduces the increased mono- and polysynaptic reflex activity in a dose-dependent manner to the physiological level. This effect is well demonstrated in several animal models.
- Central-reticular level - An imbalance between supraspinal facilitatory and inhibitory control can also lead to an enhanced reflex activity and an increased muscle tone. Tolperisone reduces the reticulo-spinal facilitation in the brainstem and has been shown to be effective in alleviating experimental gamma-rigor of reticular origin. The blood flow enhancing effect of tolperisone is still not understood. Involvement of calcium-antagonistic, slight spasmolytic or slight anti-adrenergic effects have been proposed.

Diclofenac Sodium

Mechanism of action
Diclofenac sodium is a non-steroidal compound with pronounced antirheumatic, antiinflammatory, analgesic and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain and fever.

Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to those reached in humans.

Pharmacodynamic effects
In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac sodium elicit a clinical response characterised by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function.

In post-traumatic and post-operative inflammatory conditions, diclofenac sodium relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema.

Diclofenac Sodium 100 mg is particularly suitable for patients in whom a daily dose 100 mg is appropriate to the clinical picture. The possibility of prescribing the medicinal product in a single daily dose considerably simplifies long-tem treatment and helps to avoid the possibility of dosage errors.

Pharmacokinetic properties
Tolperisone
Absorption
The absorption of orally administered tolperisone from the small intestine is good. Peak plasma concentration is observed 0.5 – 1 hour after the oral intake. Bioavailability is about 20% due to significant first-pass metabolism.

Biotransformation
Tolperisone is extensively metabolised in the liver and kidneys. There are no observations that suggest a pharmacological activity of the metabolites.
In animal studies on distribution, relative accumulation of tolperisone was observed in the diencephalon, pons and medulla oblongata, as well as in the main organs of elimination such as liver and kidney.

Elimination
Tolperisone and its metabolites are excreted almost entirely through the kidneys. 98% of the administered dose is excreted with the urine within 24 hours. Less than 0.1% of the dose is eliminated in the intact form. When administered orally, the elimination half-life of tolperisone in men was calculated to be approximately 2-4 hours with a large inter-individual variation. Tolperisone is reported to have a relatively high volume of distribution (5l/kg b.w.); the total plasma clearance is 1.9±0.4 l/h/kg. The overall binding rate of tolperisone racemate to human plasma proteins is 95%.

Food increases the bioavailability.
High-fat meal increases the bioavailability of orally administered tolperisone by approx. 100% and increases the peak plasma concentration by approx. 45% as compared with fasting condition, delaying time to peak by approx. 30 minutes. Therefore, it is recommended to take Tolperisone tablets after meals.

Diclofenac Sodium

Absorption

Judged by urinary recovery of unchanged diclofenac and its hydroxylated metabolites, the same amount of diclofenac is released and absorbed from diclofenac sodium SR tablets as from enteric coated tablets. However, the systemic availability of diclofenac from diclofenac sodium SR tablets is on average about 82% of that achieved with the same dose of diclofenac sodium enteric-coated tablets (possibly due to release-rate dependent "first-pass" metabolism). As a result of a slower release of the active substance from diclofenac sodium SR tablets, peak concentrations attained are lower than those observed following the administration of gastro-resistant tablets.

Mean peak concentrations of 0.5 micrograms/mL or 0.4 micrograms/mL (1.6 or 1.25 micro mol/L) are reached on average 4 hours after ingestion of a prolonged-release tablet of 100 mg. Food has no clinically relevant influence on the absorption and systemic availability of diclofenac sodium SR tablets.

On the other hand, mean plasma concentrations of 13 ng/mL (40 nmol/L) can be recorded at 24 hours (16 hours) after administration of diclofenac sodium 100 mg. The amount absorbed is linearly related to the dose strength.

Since about half of diclofenac is metabolised during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) following oral or rectal administration is about half that following an equivalent parenteral dose.

Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

Trough concentrations are around 22 ng/mL or 25 ng/mL (70 nmol/L or 80 nmol/L) during treatment with Diclofenac sodium prolonged-release tablets 100 mg once daily.

Distribution

99.7% of diclofenac is bound to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution calculated is 0.12 to 0.17 L/kg. Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma values, concentrations of the active substance are already higher in the synovial fluid than in the plasma, and they remain higher for up to 12 hours.

Biotransformation

Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-,4'-hydroxy-,5-hydroxy-,4',5-dihydroxy- and 3'-hydroxy-4'-methoxydiclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much smaller extent than diclofenac.

Elimination

Total systemic clearance of diclofenac from plasma is 263 ±56 mL/min (mean value ±SD). The terminal half-life in plasma is 1 to 2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 3 hours. One metabolite, 3'-hydroxy-4'-methoxydiclofenac has a much longer plasma half-life. However, this metabolite is virtually inactive.

About 60% of the administered dose is excreted in the urine as the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Characteristics in patients

No relevant age-dependent differences in the drug's absorption, metabolism or excretion have been observed. In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of <10 mL/min, the calculated steady-state plasma levels of the hydroxyl metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile. In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

PRECLINICAL SAFETY DATA

Tolperisone

In acute animal toxicity studies large doses of tolperisone caused ataxia, tonic-clonic seizures, dysnpoea and respiratory failure were reported. Based on animal studies tolperisone is not teratogenic. Embryotoxic variations were observed in rats at 500 mg/kg and in rabbits at 250 mg/kg oral doses. These doses were multiple times higher than the doses applied in humans.

EXPIRY DATE

Do not use later than date of expiry

STORAGE

Store protected from light & moisture, at a temperature not exceeding 25^0C
Keep all medicines out of reach of children.

PRESENTATION

Texxa D is packed in 10 blister strips of 5 tablets each

MARKETED BY

torrent PHARMA

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

IN/TEXXA-D 450,100 mg /DEC-18/01/PI