SUMMARY OF PRODUCT CHARACTERISTIC

1. NAME OF THE PHARMACEUTICAL PRODUCT

DEKSIT 25 mg/8 mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients:

Each tablet contains 36.90 mg dexketoprofen trometamol equivalent to 25 mg dexketoprofen.and 8 mg thiocolchicoside.

Excipients:

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet.

It has the appearance of a yellowish, round, flat notched tablet. The notch makes it easier to divide the tablet into 2 equal parts.

4. CLINICAL PROPERTIES

4.1. Therapeutic indications

DEKSIT is indicated for osteoarthritis, painful syndromes of the vertebral column, extra-articular rheumatism, painful muscle spasms, post-traumatic and postoperative pain.

4.2. Posology and method of application

Posology / application frequency and duration

The recommended and daily maximum dose is one tablet (25 mg / 8 mg) every 12 hours (2 times a day), i.e. no more than 2 (50 mg / 16 mg dexketoprofen / thiocolchicoside / day) tablets per day.

The recommended duration of treatment is 5-7 days, the total duration of treatment is limited to 7 consecutive days. Avoid exceeding recommended doses or long-term use.

Method of Application:

For oral use only.

Tablets should be taken full stomach with a glass of water (150 mL).

If diarrhea occurs after oral administration, treatment should be discontinued.

Additional information on special populations:

Kidney / Liver failure:

Dexketoprofen

In patients with mild renal dysfunction (creatinine clearance 50-80 mL / min), the initial dose should be reduced to a total daily dose of 50 mg. Dexketoprofen should not be used in patients with moderate to severe renal impairment (creatinine clearance <50 mL / min).

Patients with mild or moderate hepatic impairment should start treatment at low doses (50 mg total daily dose) and be closely monitored. Dexketoprofen should not be used in patients with severe hepatic dysfunction.

Thiocolchicoside

The safety and efficacy of thiocolchicoside in patients with kidney / liver failure have not been studied.

Pediatric population:

Dexketoprofen

Since no studies have been conducted to determine the safety and efficacy of dexketoprofen in children and adolescents, its use is not recommended in children under 18 years of age.

DEKSIT should not be used in children under 18 years of age.

Geriatric population:

Dexketoprofen

It is recommended to start dexketoprofen therapy in the elderly patients at the lowest dosage range (50 mg total daily dose). After confirming that they show good tolerance, the dosage can be increased to the amounts recommended for the general population.

Thiocolchicoside

The safety and efficacy of thiocolchicoside in elderly patients has not been studied.

Patients should be monitored regularly for bleeding that may occur in the Gastrointestinal System (GIS) during treatment with drugs containing non-steroidal anti-inflammatory drugs (NSAIDs).

4.3. Contraindications

DEKSIT is contraindicated in the following cases:

- Patients with hypersensitivity to dexketoprofen, thiocolchicoside, other NSAIDs or any excipient in the content of DEKSIT,
- In loose paralysis, muscle hypotonia,

- In patients with bleeding problems and using anticoagulant drugs,
- In patients with gastrointestinal bleeding or other active bleeding or bleeding disorders,
- Patients with active or suspected peptic ulcer / bleeding or patients with recurrent peptic ulcer / bleeding (two or more different episodes of proven ulcer or bleeding) or chronic dyspepsia,
- Patients with a history of gastrointestinal bleeding or puncture related to previous NSAID therapy,
- In patients with Crohn's disease or ulcerative colitis,
- Patients with a history of bronchial asthma,
- In patients with severe heart failure,
- Patients with moderate or severe renal dysfunction,
- In patients with severe liver dysfunction,
- In patients with hemorrhagic diathesis or other clotting disorders,
- Treatment of perioperative pain in case of coronary artery bypass graft (CABG) surgery (see section 4.4),
- During the whole pregnancy and lactation,
- Contraindicated in women of childbearing potential and who do not use effective contraception (see section 4.6),
- In patients 18 and under,
- It should not be used by patients with a history of asthma, urticaria or an allergic reaction as a result of taking aspirin or other NSAIDs. In such patients, severe, rarely fatal, anaphylaxis-like reactions due to NSAID have been reported (see section 4.4).

4.4. Special use warnings and precautions

Dexketoprofen

Cardiovascular (CV) risks:

-NSAIDs can cause an increased risk of CV thrombotic events, myocardial infarction and stroke, which can be fatal. This risk may increase depending on the duration of use. The risk may be higher in patients with CV disease or patients with CV disease risk factors. DEKSIT TABLET is contraindicated in the treatment of preoperative pain coronary artery bypass surgery.

Gastrointestinal (GI) risks:

NSAIDs cause serious GI adverse effects such as bleeding, ulceration, stomach or intestinal perforation. These adverse events can occur at any time, with or without prior warning symptoms. Elderly patients have a higher risk of serious GI effects.

Warnings:

The safety of dexketoprofen in children and adolescents has not been established.

Caution should be exercised when using in patients with a history of allergic conditions.

The incidence of undesirable effects is high in the elderly with NSAIDs. Treatment should be initiated at low doses in these patients.

Concomitant use of DEKSIT with other NSAIDs, including selective cyclooxygenase-2 (COX-2) inhibitors, should be avoided. Undesirable effects can be minimized by using the lowest dose that is effective for the shortest time required to control symptoms (see Section 4.2).

Gastrointestinal (GI) effects-GI ulceration, bleeding or perforation risk:

NSAIDs, including dexketoprofen, can cause serious GI adverse effects, such as inflammation, bleeding, ulceration or perforation, in the stomach, small intestine, or large intestine. Only one in five patients who develop a serious GI adverse event during treatment with an NSAID is symptomatic. Upper GI ulcers, major bleeding or perforations due to NSAIDs occur in approximately 1% of patients treated for 3 to 6 months, and between 2% and 4% of patients treated for one year. These trends continue with increased duration of use and increase the likelihood that a patient will develop a serious GI event at some point during treatment. However, even short-term treatment is not without risk.

Extreme caution should be exercised when prescribing NSAIDs to patients with a prior history of ulcer disease or GI bleeding. Studies have shown that patients using NSAIDs, who have a history of peptic ulcer and / or GI bleeding, have a 10-fold higher risk of developing GI bleeding compared to patients without these risk factors. In addition to the ulcer story, many conditions that may increase the risk of GI bleeding have been identified, which may lead to many treatments and comorbidities, such as: treatment with oral corticosteroids, treatment with anticoagulants (warfarin) or antiplatelet agents (aspirin), treatment with selective serotonin reuptake inhibitors, prolonged treatment with NSAIDs, smoking, alcohol use, advanced age, and poor overall health. Most of the spontaneous reports on fatal GI events have been reported by elderly and weaker patients; therefore, special care must be taken when administering treatment in this population.

To minimize the potential risk of a GI-related adverse event, patients should be treated with the lowest effective dose of an NSAID for the shortest possible duration. Patients and physicians should be alert for signs of GI ulceration with bleeding and symptoms during NSAID therapy,

and if serious GI events are suspected, prompt evaluation and additional therapy should be initiated. If serious adverse events do not disappear, NSAID therapy should be stopped. Alternative treatments without NSAIDs should be considered in patients at high risk.

Whether with or without warning symptoms or a serious history of GI event, GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs. Treatment should be discontinued when GI bleeding or ulceration occurs in patients receiving DEKSIT.

The risk of gastrointestinal bleeding, ulceration or perforation increases with increasing NSAIDs, especially in patients with a history of ulcers complicated by bleeding or puncture (see section 4.3) and in the elderly.

Elderly: In the elderly, there is an increase in the frequency of adverse reactions of NSAIDs, especially fatal gastrointestinal bleeding and perforation (see section 4.2). These patients should begin treatment at the lowest possible dose.

As with all NSAIDs, any history of esophagitis, gastritis and / or peptic ulcer should be investigated to ensure complete recovery before starting dexketoprofen trometamol treatment. Patients with gastrointestinal symptoms or a history of gastrointestinal disease should be monitored for digestive disorders, especially gastrointestinal bleeding.

NSAIDs should be given with caution to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease), as they can increase the severity of their disease (see section 4.8).

In these patients, as well as in patients requiring concomitant low-dose acetylsalicylic acid or other drugs likely to increase the risk of gastrointestinal bleeding, additional treatment with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered.

Patients with a history of gastrointestinal toxicity, especially the elderly, should report abnormal abdominal symptoms (especially gastrointestinal bleeding), especially at the initial stage of treatment.

Caution is advised in patients taking oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors, or antiplatelet drugs such as acetylsalicylic acid, which may increase the risk of ulceration or bleeding (see section 4.5).

All non-selective NSAIDs can inhibit platelet aggregation and prolong bleeding time through

inhibition of prostaglandin synthesis. Therefore, patients treated with warfarin or other coumarins or heparins that affect hemostasis are not recommended to use dexketoprofen trometamol.

Renal effects:

Long-term use of NSAIDs leads to renal papillary necrosis and other renal damage. Additionally, renal toxicity has been observed in patients, since renal prostaglandins play a compensating role in the maintenance of renal perfusion. In such patients, administration of NSAIDs may result in a dose-related decrease in prostaglandin formulation and secondaryly renal blood flow, which can accelerate apparent renal decompensation. Patients at risk include those with renal insufficiency, heart failure, liver dysfunction, those taking diuretics and angiotensin converting enzyme (ACE) inhibitors, and the elderly. After discontinuation of NSAID therapy, recovery to pretreatment status is usually achieved.

Like all NSAIDs, DEKSIT can increase plasma urea nitrogen and creatinine. Like other prostaglandin synthesis inhibitors may be associated with undesirable effects on the renal system, which can lead to glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotine syndrome, and acute renal failure.

Advanced kidney diseases:

There is no information from controlled studies on the use of dexketoprofen trometamol in patients with advanced kidney disease. Therefore, DEKSIT treatment is not recommended in patients with advanced kidney disease. If DEKSIT treatment is initiated, it is recommended to closely monitor the renal functions of the patient.

Cardiovascular thrombotic events:

An increased risk of severe cardiovascular (CV) thrombotic events, myocardial infarction and stroke has been shown in clinical studies of up to 3 years, performed with a large number of selective COX-2 and non-selective NSAID. All COX-2 selective and non-selective NSAIDs may have similar risks. Patients with known cardiovascular disease or known to be at risk of cardiovascular disease may be at a higher risk. The lowest effective dose should be used for the shortest time possible to reduce the risk of adverse cardiovascular events in patients receiving NSAID therapy. The physician and patient should be vigilant against such events, even if there is no pre-seen cardiovascular symptom. The patient should be informed about the serious cardiovascular events symptoms and / or signs and what to do if they occur.

There is no consistent evidence that concomitant use of aspirin reduces the increased risk of serious cardiovascular thrombotic events associated with NSAID use. Simultaneous use of NSAIDs with aspirin increases the risk of serious GI events (see section 4.4).

In the first 10-14 days following the coronary artery bypass graft (CABG) surgery, two large, controlled clinical trials performed about a COX-2 selective NSAID for a pain relief treatment showed an increase in the incidence of myocardial infarction and stroke (see section 4.3. Contraindications).

An increased incidence of myocardial infarction and stroke was seen in two large, controlled clinical trials of a COX-2 selective NSAID given for pain relief in the first 10-14 days following coronary artery bypass graft (CABG) surgery (see section 4.3).

Patients diagnosed with uncontrolled hypertension, congestive heart failure, ischemic heart disease, peripheral artery disease and/or cerebrovascular disease should be treated with DEXIT after careful consideration.

Hypertension:

As with all other NSAIDs, dexketoprofen trometamol may cause hypertension or worsening of pre-existing hypertension, and both conditions increase the risk of cardiovascular events. Patients treated with thiazide group diuretics or loop (fold) diuretics may disrupt diuretic treatment responses when using NSAIDs. NSAIDs, including dexketoprofen trometamol, should be used with caution in patients with hypertension. Blood pressure should be closely monitored at the beginning of dexketoprofen trometamol therapy and throughout the course of treatment.

Congestive heart failure and edema:

Fluid retention and edema have been observed in some patients treated with NSAIDs, including dexketoprofen trometamol. Therefore, DEKSIT should be used with caution in patients with fluid retention or heart failure.

Appropriate monitoring and recommendations are required in patients with a history of hypertension and / or mild to moderate congestive heart failure, since fluid retention and edema have been reported in relation to NSAID therapy.

Elderly patients are more likely to develop kidney, cardiovascular or liver dysfunction (see section 4.2).

Clinical studies and epidemiological data suggest that the use of some NSAIDs (especially, at

high doses and long-term therapy) may be associated with a small increase in the risk of arterial thrombotic events (especially myocardial infarction or stroke). Data are insufficient to exclude such a risk for dexketoprofen trometamol.

Patients with uncontrolled hypertension, congestive heart failure, diagnosed ischemic heart disease, peripheral artery disease and / or cerebrovascular disease should be treated with dexketoprofen tromethamol after careful evaluation. In patients with cardiovascular risk factors, attention should also be paid before starting long-term treatment (eg hypertension, hyperlipidemia, diabetes mellitus, smoking).

Anaphylactoid reactions:
In rare cases with dexketoprofen trometamol, as with other NSAIDs, allergic reactions, including anaphylactic / anaphylactoid reactions, may occur without previous exposure to the drug. DEKSIT should not be given to patients with aspirin triad. This symptom complex typically occurs in asthmatic patients with bronchial asthma, vasomotor rhinitis, and nasal polyposis who present with severe and potentially fatal bronchospasm following aspirin or NSAID use (see. Chapter 4.3 and Chapter 4.4). Urgent help should be given when anaphylactoid reaction is seen.

Skin reactions:
Serious skin reactions including rare exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in relation to the use of NSAIDs, including dexketoprofen trometamol. These serious events can occur without warning. Reactions appear to begin within the first month of treatment. Patients should be informed of the signs and symptoms of serious skin reactions and instructed to discontinue the drug if skin rash or any other signs of hypersensitivity occur.

Pregnancy:
Like other NSAIDs, dexketoprofen trometamol should not be used in late pregnancy, as it can cause early closing of ductus arteriosus (the opening between the two major arteries [the aorta and the pulmonary artery] that emerges from the heart and should be closed after birth).

Fertility:
As with other NSAIDs, the use of dexketoprofen trometamol may impair female fertility and is not recommended in women attempting to conceive. In those who have difficulty conceiving or are undergoing infertility treatment, discontinuation of dexketoprofen trometamol should be considered.

Precautions:

General:

Dexketoprofen trometamol should not be expected to replace corticosteroids or treat corticosteroid deficiency. Abrupt stopping of corticosteroids can cause an exacerbation of the disease. Patients undergoing long-term corticosteroid therapy should reduce their treatment slowly and gradually if it is decided to stop corticosteroid therapy.

The pharmacological activity of dexketoprofen trometamol [fever and] in reducing the inflammation of DEKSIT can reduce the benefits of these diagnostic symptoms used to diagnose complications of painful conditions thought to be non-infectious.

DEKSIT should be used with caution in patients with hematopoietic disorders, systemic lupus erythematosus or mixed connective tissue disease.

Hepatic effects:

Up to 15% of patients taking NSAIDs, including dexketoprofen trometamol, may experience increases in limit level in one or more liver tests. These laboratory anomalies may progress, remain unchanged, or pass spontaneously when treatment is continued. Significant increases in ALT and AST levels (three times or more than the upper limit of normal level) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis, and liver failure, have also been reported.

During long-term treatment with dexketoprofen trometamol, as a precautionary measure, regular monitoring of liver function is required. Treatment with DEKSIT should be discontinued if abnormal liver function tests persist or worsen, clinical signs or symptoms appropriate to liver disease develop, or other symptoms (such as eosinophilia, skin rashes, etc.).

Hematological effects:

Anemia is sometimes seen in patients taking NSAIDs, including dexketoprofen trometamol. This may be due to fluid retention, occult or gross GI blood loss, or an ill-defined effect on erythropoiesis. Patients receiving long-term therapy with NSAIDs, including DEXID, should have their hemoglobin and hematocrit levels checked regularly, even if they do not have any signs or symptoms of anemia.

NSAIDs have been shown to prolong bleeding time, which inhibits platelet aggregation in some patients. Unlike aspirin, their effects on platelet function are qualitatively less, shorter and

reversible. Patients with previous coagulation disorders or who are using anticoagulants and who may be adversely affected by platelet function changes should be carefully monitored during the use of DEKSIT.

Pre-existing asthma:

Asthmatic patients may have aspirin-sensitive asthma. Aspirin use in aspirin-sensitive asthmatic patients has been associated with severe bronchospasm, which can be fatal. Since cross-reactivity including aspirin and other NSAIDs, including bronchospasm, has been reported in these patients with aspirin sensitivity, DEKSIT should not be given to patients with this form of aspirin sensitivity and should be used with caution in patients with asthma beforehand.

Information for patients

DEKSIT, like other NSAIDs, can cause serious cardiovascular side-effects such as myocardial infarction or stroke, which may result in hospitalization and even death. Although serious cardiovascular events can occur without warning symptoms, patients should be alert for signs and symptoms such as chest pain, shortness of breath, fatigue, slurred speech, and should seek medical advice if they experience any such signs or symptoms. The importance of such monitoring should be emphasized to patients (see section 4.4).

Like other drugs in this class, DEKSIT can cause discomfort and, rarely, serious side effects such as gastrointestinal ulcers and bleeding, which may require hospitalization and can even be fatal.

Because serious gastrointestinal ulceration and bleeding can occur without warning symptoms, physicians should caution patients on chronic therapy to be alert for signs and symptoms of ulceration and bleeding and to monitor for any signs or symptoms, including epigastric pain, dyspepsia, melena, and hematemesis, and to instruct them on the importance of such monitoring (see section 4.4).

Dexketoprofen, like other NSAIDs, can cause serious skin side effects, including exfoliative dermatitis, Stevens Johnson syndrome, and Toxic Epidermal Necrolysis, which can require hospitalization and can even be fatal. Although serious skin reactions can occur without warning, patients should be alert for other signs and symptoms of hypersensitivity, such as skin rash and vesicles, fever, or itching, and should seek medical attention if they experience any signs or symptoms. Patients should be instructed to stop taking the medication immediately and consult their physician as soon as possible if any type of rash occurs.

Patients should be instructed to promptly report any signs and symptoms of unexplained weight gain or edema to their physician.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and flu-like syndrome). If these occur, patients should be instructed to stop therapy and seek immediate medical attention.

Patients should also be advised to seek immediate medical attention if an anaphylactoid reaction occurs (e.g. difficulty breathing, swelling of the face or throat) (see section 4.4). DESKIT, like other NSAIDs, should not be taken in late pregnancy because it will cause premature closure of the ductus arteriosus.

Laboratory tests:
Physicians should monitor patients for the signs or symptoms of GI bleeding, as severe GI system ulcerations and bleeding can occur without warning symptoms. Complete blood count and biochemistry profiles of patients receiving long-term NSAID therapy should be checked periodically. If clinical signs and symptoms compatible with liver develop, or systemic symptoms (eg eosinophilia, rash, etc.) occur, or liver test results become abnormal or worsen, DEKSIT intake should be stopped.

Thiocolchicoside
Preclinical studies have shown that one of thiocolchicoside metabolites (SL59.0955) at concentrations close to human exposure, observed at doses of 8 mg twice daily, induces aneuploidy (ie, unequal chromosome number in dividing cells) (see section 5.3). Teratogenicity of aneuploidy appears to be a risk factor for embryotoxicity/fetotoxicity - spontaneous abortion and impaired male fertility, and a potential risk factor for cancer. For therapeutic purposes, use of the product in doses exceeding the recommended dose or long-term use should be avoided (See Section 4.2).

In post-marketing experience, cytolytic and cholestatic hepatitis with thiocolchicoside has been reported. Severe cases (eg fulminant hepatitis) have been reported in patients taking NSAIDs or paracetamol simultaneously. Patients should be warned to promptly report symptoms that may be related to liver toxicity (see section 4.8).

The use of thiocolchicoside in children is not recommended.

Thiocolchicoside can accelerate seizures, especially in patients with epilepsy or in patients at risk

of seizures (see section 4.8).

Patients should be carefully informed about the potential risk of pregnancy and effective contraception methods to be followed.

In case of diarrhea following oral administration, thiocolchicoside therapy should be discontinued.

4.5. Interactions with other medicinal products and other forms of interaction

Dexketoprofen

Combinations not recommended:

– Other NSAIDs, including high-dose salicylates (≥ 3 g/day):

Concomitant administration with some NSAIDs may increase the risk of gastrointestinal ulcers and bleeding through synergistic effects.

– Aspirin: When dexketoprofen is given with aspirin, protein binding rate decreases even though free dexketoprofen clearance does not change. Although the clinical significance of this interaction is unknown, as with other NSAIDs, concomitant administration of dexketoprofen and aspirin is not generally recommended as it increases the likelihood of adverse effects.

– Anticoagulants: NSAIDs may increase the effects of anticoagulants such as warfarin (see section 4.4) due to high plasma protein binding of dexketoprofen, inhibition of platelet function, and gastroduodenal mucosa damageIf this combination cannot be avoided, close clinical observation and laboratory values should be followed.

– Warfarin: The effect of warfarin and NSAIDs on GI bleeding is synergistic; that is, patients who use these two drugs together are at a higher risk of developing severe GI bleeding than those who use these two drugs alone.

– Heparin: The risk of hemorrhage increases (due to inhibition of platelet function and gastroduodenal mucosa damage). If the combination cannot be avoided, close clinical observation and laboratory values should be followed.

– Corticosteroids: There is an increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

– Lithium (defined by many NSAIDs): NSAIDs lead to an increase in plasma lithium levels and a decrease in renal lithium clearance. The average minimum lithium concentration increased by

15% and renal clearance decreased by about 20%. These effects are attributed to the inhibition of renal prostaglandin synthesis by NSAIDs. Therefore, when NSAIDs and lithium are given simultaneously, the patient should be carefully monitored for lithium toxicity.

- Methotrexate, 15 mg / week or higher doses: In general, an increase in hematological toxicity is observed due to the reduction of renal clearance of methotrexate with anti-inflammatory agents. NSAIDs have been reported to inhibit methotrexate accumulation competitively in rabbit kidney sections. This indicates that NSAIDs may increase methotrexate toxicity. Caution should be exercised if NSAIDs are administered at the same time with methotrexate.

- Hidantoins and sulfonamides**:** Toxic effects of these compounds may increase.

Combinations that need attention:

- Diuretics, ACE inhibitors and angiotensin II receptor antagonists and aminoglycoside antibacterials: Dexketoprofen can reduce the effect of diuretics and antihypertensive products. It is stated in the current reports that NSAIDs can reduce the antihypertensive effect of ACE-inhibitors. This interaction should be considered in patients taking NSAIDs with ACE-inhibitors. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the concomitant use of agents that inhibit cyclooxygenase and ACE inhibitors or angiotensin II receptor antagonists may result in further deterioration of renal function, which is usually reversible. In cases where dexketoprofen is prescribed together with a diuretic, patients should be adequately hydrated and renal function monitored at the start of treatment, as diuretics may increase the risk of nephrotoxicity of NSAIDs (see section 4.4).
- Furosemide: Clinical studies and post-marketing observations show that the use of dexketoprofen can reduce the natriuretic effect of furosemide and thiazides in some patients.. This response is attributed to the inhibition of renal prostaglandin synthesis. When treatment with NSAIDs is administered simultaneously, the patient should be closely monitored for signs of kidney failure (see section 4.4) and to ensure diuretic effectiveness.

- Using methotrexate at doses less than 15 mg / week: Usually, hematological toxicity increases due to reduction of renal clearance with anti-inflammatory compounds. Blood counts should be monitored weekly during the first weeks of the combination. In cases where renal functions are slightly impaired and also in the elderly, monitoring should be increased.

- Pentoxifylline: Increases the risk of bleeding. Clinical monitoring should be increased and bleeding time should be checked more frequently.

- Zidovudine: Increased erythrocyte toxicity via reticulocytes is observed, with severe anemia occurring one week after starting NSAID intake. Complete blood count and reticulocyte count should be checked two weeks after starting treatment with NSAIDs.

- Sulfonylureas: NSAIDs can increase their hypoglycemic effects by removing sulfonylureas from their binding sites to plasma proteins (very rare).

Combinations to be consider:

- Beta blockers: Treatment with an NSAID may reduce antihypertensive effects by inhibition in prostaglandin synthesis.
- Cyclosporine and tacrolimus: Nephrotoxicity may increase with the effects of NSAIDs mediated by renal prostaglandin synthesis inhibition. Renal functions should be calculated during combination therapy.
- Thrombolytics: Increases the risk of bleeding.
- Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): Increases the risk of gastrointestinal bleeding (see section 4.4).
- Probenecid: The plasma concentrations of dexketoprofen may increase; this interaction may be due to an inhibitory mechanism and glucuronide conjugation in the renal tubular secretion region and requires adjustment of the dose of dexketoprofen.
- Cardiac glycosides: NSAIDs can worsen heart failure, reduce glomerular filtration rate (GFR), and increase plasma glycoside levels.
- Mifepristone: NSAIDs should not be used within 8-12 days after taking mifepristone, as prostaglandin synthetase inhibitors theoretically have the risk of modifying the effectiveness of mifepristone.
- Quinolone antibiotics: Data from animal studies show that high doses of quinolone intake with NSAIDs may increase the risk of developing convulsions.

Thiocolchicoside

Considering recent clinical experience, thiocolchicoside, non-steroidal anti-inflammatory agents, phenylbutazone, analgesics and preparations using in neurite treatment are successfully and safely combined with anabolic steroids, sedatives, barbiturates and succinylcholine.

Taking thiocolchicoside with other drugs that have a muscle relaxant effect on the musculoskeletal system is not recommended because they may increase the effect of each other. For the same reason, if it is used with another drug acting on smooth muscles, more attention should be paid and the patient should be observed in case the frequency of undesired effects increases.

Thiocolchicoside should not be used with anticoagulants.

Additional information on special populations

No interaction studies have been conducted on special populations.

Pediatric population:

The interaction study of dexketoprofen and thiocolchicoside combination has not been conducted. Also, there are no studies in children and adolescents. Therefore, its reliability and effectiveness have not been proven. Should not be used in children under 18.

4.6. Pregnancy and lactation

General advise

Pregnancy category is X.

Women with childbearing potential / Contraception (Contraception)

DEKSIT is contraindicated during pregnancy (see section 4.3).

Women of childbearing potential must use effective birth control during treatment.

Gestation period

Dexketoprofen

Inhibition of prostaglandin synthesis may affect pregnancy and/or embryo/fetal development. Data from epidemiology studies have shown an increased risk of gastrosis, cardiac malformations and miscarriage after use of prostaglandin synthesis inhibitors in early pregnancy. The risk of cardiac malformations was less than 1% and increased to approximately 1.5%. It is believed that the risk may increase with dose and duration of treatment. Animal studies have shown that use of prostaglandin synthesis inhibitors causes increased pre- and post-implantation loss and embryo-fetal death. Prostaglandin synthesis inhibitors administered to animals during the organogenic process increased the incidence of various malformations, including cardiovascular. Animal studies with dexketoprofen trometamol did not show reproductive

toxicity.
In the first and second trimester of pregnancy, dexketoprofen trometamol should not be given unless clearly needed. If dexketoprofen trometamol is used by a woman trying to conceive or in the first and second trimesters of pregnancy, the dose should be kept as low as possible and the duration of treatment should be as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors can have the following effects on the fetus:

- Cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension);
- Kidney dysfunction that can cause kidney failure and oligohydroamniosis;

Mother and newborn at the end of pregnancy:

- Probability of prolonged bleeding, an antiaggregant effect that can occur even at very low doses;
- Inhibition of uterine contraction, which can cause delayed or prolonged labor

Thiocolchicoside
Animal studies have shown reproductive toxicity, including teratogenic effects (see section 5.3). There are insufficient clinical data to assess the safety of use during pregnancy. Therefore, the potential hazards to the embryo or fetus are unknown. Consequently, thiocolchicoside is contraindicated during pregnancy and in women of childbearing potential who are not using effective contraception (see section 4.3).
Consequently, DEXIT is contraindicated during pregnancy (see section 4.3.).

Lactation period

Although NSAIDs may be seen in breast milk at very low concentrations in limited studies to date, it is not known whether dexketoprofen passes into breast milk. Thiocolchicoside use is contraindicated during breastfeeding due to its passage into breast milk (see section 4.3).

Reproductive ability / Fertility

Along with other NSAIDs, the use of dexketoprofen trometamol may affect fertility and is not recommended for women trying to conceive. In women who have difficulty conceiving or have been investigated for infertility, discontinuation of dexketoprofen trometamol should be considered. Dexketoprofen trometamol should not be used in the first and second trimesters of pregnancy unless clearly mandatory.

In the fertility study on rats, no fertility deterioration was observed at doses up to 12 mg / kg - at dose levels that did not induce any clinical effects. Thiocolchicoside and its metabolites show aneugenic activity at different concentration levels (see Genotoxicity), which is a risk factor for impairment of human fertility (see section 4.4). As a precaution, the use of the product in doses higher than recommended or for long periods should be avoided (see section 4.2).

4.7. Effects on the ability to drive and use machines

Since DEXIT may cause undesirable effects such as dizziness, somnolence, vertigo, weakness and visual disturbances after taking it, it may have mild or moderate effects on the ability to use machines or vehicles. Caution should be exercised when using machines or vehicles or the use of machines or vehicles should be avoided.

4.8. Undesirable effects

Adverse effects reported due to the separate use of dexketoprofen trometamol and thiocolchicoside are listed below.:

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); unknown (cannot be estimated from the available data).

Blood and lymphatic system disorders

Very rare: Neutropenia, thrombocytopenia

Immune system diseases

Rare: Laryngeal edema

Very rare: Anaphylactic reaction, including anaphylactic shock

Metabolism and nutritional diseases

Rare: Anorexia

Psychiatric diseases

Uncommon: Insomnia, anxiety

Nervous system disorders

Uncommon: headache, lightheadedness, somnolence

Rare: paraesthesia, syncope

Eye diseases

Very rare: blurred vision

Ear and labyrinth disorders

Uncommon: Vertigo

Very rare: Tinnitus

Cardiac diseases

Uncommon: Palpitations

Very rare: Tachycardia

Vascular diseases

Uncommon: Flushing

Rare: hypertension

Very rare: Hypotension

Respiratory, thoracic and mediastinal diseases

Rare: Bradipne

Very rare: Bronchospasm, dyspnea

Respiratory, thoracic and mediastinal disorders

Rare: Bradypnea

Very rare: Bronchospasm, dyspnea

Gastrointestinal diseases

Common: Nausea and / or vomiting, abdominal pain, diarrhea, dyspepsia

Uncommon: Gastritis, constipation, dry mouth, flatulence

Rare: Peptic ulcer, peptic ulcer bleeding or perforation (see section 4.4).

Very rare: Pancreatitis

Hepato-biliary diseases

Rare: Hepatitis

Very rare: Hepatocellular damage

Skin and subcutaneous tissue disorders

Uncommon: skin rashes

Rare: urticaria, acne, increased sweating.

Very rare: Stevens Johnson syndrome, toxic epidermal necrolysis (Lyell syndrome) angioneurotic edema, facial edema, photosensitivity reactions, itching

Musculoskeletal and Connective Tissue Disorders

Rare: back pain

Kidney and urinary tract diseases

Rare: Polyuria, acute renal failure

Very rare: Nephritis or nephrotic syndrome

Reproductive system and breast disorders

Rare: Menstrual

Reproductive system and breast diseases

Rare: Menstrual disorders, prostatic disorders

General disorders and diseases related to the application site

Uncommon: Fatigue, pain, asthenia, rigor, malaise

Rare: Peripheral edema

Research

Rare: Liver function test abnormality

Gastrointestinal: The most common adverse events are gastrointestinal ones. Sometimes fatal peptic ulcer, perforation, or gastrointestinal bleeding can occur, especially in the elderly (see section 4.4). After administration, nausea, vomiting, diarrhea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, colitis and exacerbation of Crohn's disease reported (see section 4.4). Less often, gastritis has been observed. Pancreatitis has been reported very rarely.

Edema, hypertension, and heart failure have been reported in association with NSAID therapy. As with other NSAIDs, the following undesirable effects may occur: aseptic meningitis, which may be more common in patients with systemic lupus erythematosus or mixed connective tissue disease; haematological reactions (purpura, aplastic and haemolytic anaemia, and rarely agranulocytosis and medullary hypoplasia).

Bullous reactions including Steven Johnson Syndrome and Toxic Epidermal Necrolysis (very rare). Clinical trial and epidemiological data suggest that the use of some NSAIDs (particularly at high doses and with long-term therapy) may be associated with a small increased risk of arterial thrombotic events (especially myocardial infarction or stroke) (see section 4.4).

Other rarely reported adverse reactions include:

Renal: Nephrotoxicity in various forms such as interstitial nephritis, nephrotic syndrome and kidney failure.

Liver: Abnormal liver function, hepatitis and jaundice.

Neurology and sensory organs: Visual disturbances, optic neuritis, headaches, paresthesia, aseptic meningitis symptoms (especially in patients with existing autoimmune disorders such as systemic lupus erythematosus, mixed connective tissue disease), nape stiffness, headache, nausea, vomiting, fever or disorientation (see section 4.4), depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, weakness and dizziness.

Hematological events: Thrombocytopenia, neutropenia, agranulocytosis, aplastic anemia and hemolytic anemia.

Dermatological events: Bullous reactions (very rare), including Steven Johnson Syndrome and Toxic Epidermal Necrolysis. Fotosensivity.

Thiocolchicoside

Adverse effects observed in clinical studies and related to thiocolchicoside intake are listed below:

Immune system diseases
Uncommon: Pruritus
Rare: Urticaria,
Not known: Angioneurotic edema, i.m. anaphylactic shock following administration

Nervous system disorders
Common: Somnolence

Not known: Vasovagal syncope (usually occurs in minutes following the administration of i.m.), transient confusion and excitation, convulsions.

Cardiac diseases
Rare: Hypotension

Gastrointestinal diseases
Common: Diarrhea (see section 4.4), gastralgia
Rare: Nausea, vomiting

Hepatobiliary diseases
Not known: Cystolytic and cholestatic hepatitis (see section 4.4).

Skin and subcutaneous tissue disorders
Uncommon: allergic skin reaction

4.9. Overdose and treatment

Dexketoprofen

Overdose symptoms of dexketoprofen trometamol are unknown. The following have been observed in relation to NSAIDs.:

a) Symptoms

Headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhea, disorientation, excitation, coma, dizziness, stupor, tinnitus, fainting, occasional convulsions. In marked poisoning situations, acute renal failure and liver damage are possible.

b) Therapeutic measures

In case of accidental ingestion or excessive use, symptomatic treatment should be applied immediately according to the clinical condition of the patient. Activated charcoal should be considered within one hour when taken more than 5 mg / kg by an adult or a child.

Alternatively, in adults, gastric lavage should be considered within one hour in the event of a potentially life-threatening overdose. Good urine output should be provided.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after potentially toxic doses. Frequent or prolonged convulsions should be treated with intravenous diazepam.

Depending on the clinical condition of the patient, other measures may be required. Dexketoprofen trometamol can be removed from the body by dialysis.

Thiocolchicoside

No specific symptom of overdose has been reported in patients treated with thiocolchicoside.

Treatment:

In case of overdose, medical observation and symptomatic measures are recommended (see Section5.3).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Propionic acid derivatives and centrally acting myorelaxane
ATC Code: M03BX55 (Combination of dexketoprofen and Thiocolchicoside)

Dexketoprofen
Dexketoprofen trometamol S -(+)-2-(3-benzoylphenyl) tromethamine salt of propionic acid, is an analgesic, anti-inflammatory and antipyretic drug included in the non-steroidal anti-inflammatory drug group (M01A).

The mechanism of action of non-steroidal anti-inflammatory drugs is related to the reduction of prostaglandin synthesis by inhibition of the cyclooxygenase pathway. In particular, there is inhibition of the transformation of prostaglandins PGE_1, PGE_2, $PGF_{2\alpha}$ and PGD_2, as well as prostacyclin PGI_2 and thromboxanes (TxA_2 and TxB_2) into cyclic endoperoxides, PGG_2 and PGH_2. In addition, inhibition of prostaglandin synthesis affects other inflammatory mediators such as quinine, causing an indirect effect in addition to direct effect.

Dexketoprofen has been shown to be an inhibitor of COX-1 and COX-2 activities in animal and human experiments.

Clinical studies in various pain models have shown that dexketoprofen trometamol has an effective analgesic effect. The onset of analgesic effect was achieved in some studies within 30 minutes after application. Analgesic effect lasts 4-6 hours.

Thiocolchicoside
Thiocolchicoside is a semi-synthetic sulphurized colchicoside derivative with muscle relaxant pharmacological activity.

Thiocolchicoside only binds to GABAergic and striknine-sensitive glycinergic receptors in vitro. As a GABAergic receptor antagonist, thiocolchicoside may demonstrate its muscle relaxant effects by regulating complex mechanisms at the supraspinal level; however, the glycinergic mechanism of action cannot be excluded. The interaction properties of thiocolchicoside with GABAergic receptors are qualitatively and quantitatively common with its circulating main metabolite, glucuronide derivative (see Section 5.2).

Muscle relaxant properties of thiocolchicoside and its main metabolite have been demonstrated in various predictive models performed in rats and rabbits in vivo. The absence of a muscle relaxant effect in spinalized rats of thiocolchicoside indicates the dominant supraspinal effect of this compound.

In experimental studies, it has been understood that thiocolchicoside has anti-inflammatory and analgesic effects after oral, subcutaneous, intraperitoneal and intramuscular applications.

In addition, electroencephalographic (EEG) studies have shown that thiocolchicoside and its main metabolite have no sedative effects.

5.2. Pharmacokinetic properties

General properties

Absorbation:

Dexketoprofen

Deksketoprofen trometamol reaches Cmax 30 in minutes (range 15-60 minutes) after oral administration to humans. When applied with food, the AUC (area under the curve) does not change, whereas the Cmax of dexketoprofen trometamol decreases and the absorption rate is delayed (increased tmax).

Thiocolchicoside

After oral administration, thiocolchicoside is not detected in plasma. Only two metabolites are observed:

The pharmacologically active metabolite is SL18.0740 and the inactive metabolite SL59.0955. Maximum plasma concentrations for both metabolites are seen 1 hour after thiocolchicoside administration. After a single 8 mg oral thiocolchicoside dose, the C max and AUC values of SL18.0740 were about 60 ng / mL and 130 ng.hr / mL, respectively. These values are much lower for SL59.0955: C max is about 13 ng / mL; AUC ranges from 15.5 ng / h (up to 3 hours) to 39.7 ng.hr / mL (up to 24 hours).

Distribution:

Dexketoprofen

The distribution half-life of dexketoprofen trometamol is 0.35 hours. As with other drugs that show high binding (99%) to plasma proteins, the average value of the distribution

volume is less than 0.25 L / kg. In multi-dose pharmacokinetic studies, observing that the AUC after the last administration is not different from that achieved after a single dose is an indication that drug accumulation does not occur. Dexketoprofen is not involved in the accumulation of xenobiotics in adipose tissues.

Thiocolchicoside

Thiocolchicoside is bound to serum proteins at a low level in humans (13%) and this binding is not dependent on therapeutic thiocolchicoside concentration; serum protein binding is primarily mediated by serum albumin.

The apparent volume of distribution and systemic clearance of thiocolchicoside are approximately 43 L/h and 19 L/h, respectively.

Biotransformation:

Dexketoprofen

Obtaining only S - (+) enantiomer in urine after administration of dexketoprofen trometamol indicates that there is no conversion to R - (-) enantiomer in humans. In multi-dose pharmacokinetic studies, observing that the AUC after the last administration is not different from that achieved after a single dose indicates that drug accumulation does not occur.

Thiocolchicoside

After oral administration, thiocolchicoside is first metabolized to the aglycone 3 demethylthiocolchicosine (SL59.0955). This step occurs primarily by intestinal metabolism, which explains the absence of unchanged thiocolchicoside in the circulation when administered orally.

SL59.0955 is then metabolized to SL18.074, which has pharmacological activity equivalent to thiocolchicoside and thus supports the pharmacological activity of thiocolchicoside after oral administration. In addition, SL59.0955 is demethylated to didemethyl-thiocolchicine.

Elimination:

Dexketoprofen

The elimination half-life of dexketoprofen trometamol is 1.65 hours. Only the S-(+)

enantiomer is obtained in the urine after administration of dexketoprofen trometamol, indicating that the R-(-) enantiomer is not formed in humans. The major route of elimination of dexketoprofen is renal excretion followed by glucuronide conjugation.

Thiocolchicoside

After oral administration, total radioactivity is mainly excreted in faeces (79%), whereas urinary excretion is only 20%. Unchanged thiocolchicoside is not excreted through urine or faeces. While SL18.0740 and SL59.0955 are found in urine and faeces, didemetyl-thiocolchicine is only seen in faeces. After oral administration of thiocolchicoside, the SL18.0740 metabolite is eliminated with a visible t1/2 of 3.2 to 7 hours and a metabolite of SL59.0955 with an average of 0.8 hours t1/2.

Linearity / Nonlinear state:

Dexketoprofen

Dexketoprofen trometamol shows linear pharmacokinetics with a dose-dependent increase during systemic exposure following oral dose.

Thiocolchicoside

Data is not available.

Characteristic properties in patients

Dexketoprofen

Kidney failure:

In patients with mild to moderate renal impairment, after taking a single dose of 12.5 mg dexketoprofen trometamol, only increases in Cmax by 22% and 37%, respectively, compared to healthy volunteers. In general, dose adjustment is recommended for dexketoprofen in patients with renal impairment (see section 4.2).

Liver failure:

No statistically significant differences in pharmacokinetic parameters were observed in patients with mild-to-moderate hepatic impairment following single and repeated doses in comparison with healthy volunteers. In general, dose adjustment is recommended in patients with hepatic impairment (see section 4.2.).

Elders:

After oral administration of 25 mg dexketoprofen trometamol, compared to young volunteers, the AUC and half-life values of older volunteers increased by about 50%, and after single or repeated doses a 40% decrease in clearance was observed; there was no change in Tmax and Cmax. Although there is no significant drug accumulation in plasma following repeated doses, careful dose adjustment is required for this population in renal failure in elderly patients (see section 4.2).

Thiocolchicoside

No data available.

5.3. Pre-clinical safety data

Dexketoprofen

Preclinical data showed no special hazard for humans based on the classic studies of safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity, and immunopharmacology. In chronic toxicity studies on mice and monkeys, the Adverse Effect Observed Adverse Effect Level (NOAEL) was determined as 3 mg / kg / day. The main undesirable effects observed at high doses are dose-dependent gastrointestinal erosions and ulcers.

Thiocolchicoside

Acute toxicity:

Thiocolchicoside caused severe vomiting in dogs, diarrhea in rats and convulsions in both rodents and non-rodents following acute oral administration at high doses.

Chronic toxicity:

The thiocolchicoside profile was evaluated in vitro and in vivo following parenteral and oral administration.

Thiocolchicoside was well tolereted with intramuscularly administered for 4 weeks with repeated doses up to 0.5 mg / kg / day in primates and with orally administrtaion both in rats ≤2 mg / kg / daily repeat doses and in non-human primates ≤2.5 mg / kg / daily repeat doses, up to 6 months.

At high doses, after oral oral administration, thiocolchicoside induced vomiting in dogs, diarrhea in rats, and convulsions in both rodents and non-rodents.

After repeated administration, thiocolchicoside induced oral gastro-intestinal disorders (enteritis, vomiting) and vomiting intramuscularly.

Carcinogenicity:

Its carcinogenic potential has not been evaluated.

Genotoxicity:

The thiocolchicoside itself did not induce gene mutation (Ames test) in bacteria, in vitro chromosomal damage (chromosomal aberration test in human lymphocytes) and in vivo chromosomal damage (in vivo intraperitoneal micronucleus test in mouse bone marrow).

The major glucouro-conjugated metabolite SL18.0740 did not induce gene mutation (Ames test) in bacteria; however, it induced in vitro chromosomal damage (in vitro micronucleus test on human lymphocytes) and in vivo chromosomal damage (in vivo intraperitoneal micronucleus test in the orally applied mouse bone marrow). The formation of micronuclei mostly due to chromosome loss (centromer positive micronucleus after FISH centromer staining) is an indicator of aneugenic properties. The aneugenic effect of SL18.0740 was observed at higher in AUC plasma exposure (10 times higher than in AUC) than observed in therapeutic human plasma at concentrations in the in vitro test and in vitro test. Aglycone metabolite (3-demethylthiocolchicine - SL59.0955), mainly formed after anal administration, was induced in vitro chromosome damage (in vitro micronucleus test on human lymphocytes) and in vivo chromosomal damage (in vivo oral micronucleus test in the orally applied rat bone marrow). Micronuclei are mostly caused by chromosome loss (centromere positive micronuclei after FISH or CREST centromere staining), indicating aneugenic properties. The aneugenic effect of SL59.0955 was observed at concentrations in the in vitro test and at exposures in the in vivo test close to those observed in human plasma at therapeutic doses of 8 mg orally twice daily.

Aneugenic effect can cause aneuploid cell formation in division cells. Aneuploidy, when it affects germ cells, is a risk factor for teratogenicity, embryotoxicity / spontaneous abortion, impaired male fertility, and when it affects somatic cells, is a change in the number of chromosomes known as a potential risk factor for cancer and loss of heterozygosity.

Teratogenicity:

In rats, a dose of 12 mg thiocolchicoside caused major malformations along with fetotoxicity (growth retardation, embryo death, disruption in sex distribution). The dose without toxic effect is 3 mg / kg / day.

Thiocolchicoside in rabbits showed maternotoxicity starting from 24 mg / kg / day. In addition, minor abnormalities (supernumerary tooth, ossification retardation) were observed.

Fertility disorders:

In a fertility study on rats, no fertility deterioration was observed at doses up to 12 mg / kg / day, ie at dose levels that had no clinical effect. Thiocolchicoside and its metabolites show aneugenic effects at different concentration levels; this is known as a risk factor for impairment of human fertility.

6. PHARMACEUTIC PROPERTIES

6.1. List of Excipients

Partial pregelatinized corn starch
Sodium starch glycollate Type A
Microcrystalline cellulose PH 102
Microcrystalline cellulose PH 101
Magnesium stearate
Pure water

6.2. Incompatibilities

It is invalid.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at room temperature below 25ºC by protecting from moisture and light.

6.5. The nature and content of the packaging

Presented as 14 tablets with PVC / PVD / Aluminum blister packaging and carton box with

patient information leaflet.

6.6. Disposal of residual substances from the medicinal product and other special precautions

Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. MARKETING AUTHORIZATION NUMBER

Drogsan İlaçları San. ve Tic. A.Ş.
Oğuzlar Mah. 1370. Sok. No: 7/3
06520 Balgat / Ankara – Turkey

8. MARKETING AUTHORIZATION CERTIFICATE NUMBER

2017/954

9. FIRST MARKETING AUTHORIZATION CERTIFICATE DATE / MARKETING AUTHORIZATION CERTIFICATE RENEWAL DATE

First license date: 21.12.2017

License renewal date:

10. DATE OF RENEWAL OF SPC

25/05/2023