SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
ASEKET 25 mg/ 500 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains;

Active substances:

Paracetamol	500 mg
Dexketoprofen trometamol	36.9 mg (equivalent to 25 mg dexketoprofen)

Excipients:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film coated tablet
White, film coated oblong, biconvex tablets.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
It is indicated in the treatment of symptoms and findings of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis with in the treatment of acute gut arthritis, acute musculoskeletal system pains, postoperative pain and dysmenorrhea.

4.2. Posology and method of administration
Posology/frequency of administration and duration of the treatment:

Adults:
Recommended dose according to the nature and severity of the pain is one film-coated tablet in three times per day (one tablet in 8 hours).
The total daily dose of dexketoprofen should not be exceed 75 mg; the total daily dose of paracetamol should not exceed 4 g.
The daily dose of paracetamol should not exceed 2000 mg due to the risk of hepatotoxicity in alcohol users.
Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. Dosing should be decreased conveniently if diarrhea occurs following oral administration.
ASEKET are not intended for long-term use and the treatment must be limited to the symptomatic period. ASEKET should not be used more than consecutive three days without a doctor advice.

Method of administration:
ASEKET is only for oral administration.
Concomitant administration with food delays the absorption rate of the drug, thus in case of acute pain it is recommended that administration is at least 30 minutes before meals.
The tablet should be swallowed with a sufficient amount of water.

Additional information for special population:
Renal failure:
The initial dosage of dexketoprofen in ASEKET should be reduced to 50 mg total daily dose in patients with mildly impaired renal function. ASEKET should not be used in patients with moderate to severe renal dysfunction.

Hepatic failure:
Patients with mild to moderate hepatic dysfunction should start therapy at reduced doses and be closely monitored (total daily dose of dexketoprofen in ASEKET should be 50 mg). ASEKET should not be used in patients with severe hepatic dysfunction.

Pediatric population:
Dexketoprofen in ASEKET has not been studied in children and adolescents. Therefore the safety and efficacy in children and adolescents have not been established and the product should not be used in children and adolescents.

Geriatric population:
In elderly patients the recommended to initial dose for dexketoprofen in ASEKET is 50 mg total daily dose. The dosage may be increased to that recommended for the general population (75 mg) only after good general tolerance has been ascertained. No requirement of special dose adjustment for paracetamol in ASEKET in elders.

4.3. Contraindications
ASEKET should not be administered in the following cases:

- Hypersensitivity to the dexketoprofen, paracetamol, to any other NSAID, or to any of the excipients in ASEKET
- Like other NSAIDs, ASEKET also should not be used in patients that have precipitate attacks of asthma, urticaria and acute flue with the usage of NSAID drugs that inhibit acetylsalicylic acid or other prostaglandin synthetase enzyme. In these patients, it is noticed that the formation of severe, rarely fatal, anaphylaxis like reactions (see section 4.4 Special warnings and precautions for use – Anaphylactoid reactions and Pre-existing asthma).
- In the treatment of perioperative pain in case of coronary artery bypass graft (CABG) surgery (see section 4.4 Special warnings and precautions for use)
- Patients with active or suspicious peptic ulcer/history of bleeding or repeating peptic ulcer/bleeding or chronic dyspepsia
- Patients with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Patient using another drug containing paracetamol
- Patients with Crohn's disease or ulcerative colitis.
- Deficiency of Glucose 6 phosphate dehydrogenase enzyme (G6PD)
- Bronchial asthma history
- Patients with moderate or severe renal dysfunction
- Patients with severe heart failure
- Patient with severe hepatic dysfunction
- Patients with hemorrhagic diathesis and other coagulation disorders.
- During the pregnancy and lactation period

4.4. Special warnings and precautions for use
Dexketoprofen

Warnings
The safe use in children and adolescents has not been established.
Administer with caution in patients with a history of allergic conditions.
The usage with concomitant other NSAIDs including cyclooxygenase2 selective inhibitors should be avoided.

Gastrointestinal effects - gastrointestinal ulceration, bleeding or perforation risk:
All NSAIDs including dexketoprofen may cause serious gastrointestinal events like inflammation in stomach, small intestine or large intestine, bleeding, ulceration or perforation that may be fatal. These serious adverse effects may occur at any time during treatment, with or without warning symptoms in the patients under treatment with NSAIDs. During the treatment with an NSAID, only one of five patient that have a serious GI adverse event is symptomatic. Upper GI ulcer, large bleeding or perforations as a cause of NSAIDs are observed in 1% of the patients treated for 3 to 6 months duration, in 2% to 4% of the patients treated for 1 year duration. These continues intends in time increases the possibility of occurring a severe GI event in any stage of the treatment. However, even short-term treatment is not risk-free.

Nonsteroidal anti-inflammatory drugs should be prescribed with care to patients with the history of ulcer or GI bleeding before. Studies have shown that patients using NSAIDs who previously had a history of peptic ulcer and / or GI bleeding were 10 times more likely to develop GI bleeding than patients without these risk factors. Studies conducted in addition to the ulcer story, have identified a number of conditions that can lead to multiple treatments and comorbidities, such as the following, which may increase the risk of hemorrhage: treatment with oral corticosteroids, treatment with anticoagulants, prolonged treatment with NSAIDs, alcohol use, alcohol dependence and bad condition of general health. Most spontaneous reports of fatal GI events have been reported by elderly and vulnerable patients; therefore, it is necessary to be particularly careful when treating patients with such conditions.

To minimize the potential risk of an adverse GI event, patients should be treated with the shortest possible time and with the lowest effective NSAIDs. Patients and doctors should be cautious about the signs and symptoms of ulceration and hemorrhage during NSAID therapy and if it is suspected for serious GI events, an additional assessment should be made and additional treatment should be initiated immediately.

If serious adverse events do not disappeared, treatment with NSAID should be discontinued. Alternative treatments without NSAIDs should be considered in patients in the high-risk group. NSAIDs should be used with caution as patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) may be exacerbated (see section 4.8 Undesirable effects). Combination therapy should be considered for these patients and in combination with protective agents (eg, misoprostol or proton pump inhibitor) for patients with concomitant use of low-dose acetylsalicylic acid or other drugs that may increase the risk (see below and section 4.5).

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

Patients using deksketoprofen in combination with oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors and anti-thrombocytic drugs such as acetylsalicylic acid (aspirin) should be warned in advance that ulceration or bleeding may increase. All non-selective NSAIDs may inhibit platelet aggregation and prolong bleeding time by the inhibition of prostaglandin synthesis. Therefore, the use of dexketoprofen trometamol is not recommended for patients treated with warfarin or other coumarins or heparins that affect haemostasis (see section 4.5).

Renal effects:
Long-term use of NSAIDs leads to renal papillary necrosis and other renal damage. Renal toxicity has also been observed in patients, since renal prostaglandins play a compensatory role in the maintenance of renal perfusion. NSAID administration in such patients may result in a dose-dependent decrease in prostaglandin formation and, secondarily, renal blood flow, which may accelerate apparent renal decompensation. Patients with the highest risk of such a reaction are those with impaired renal function, heart failure, liver dysfunction, diuretics and ACE inhibitors and the elderly. After the NSAID therapy is stopped, it is usually returned to the pre-treatment state.

Like all NSAIDs, dexketoprofen trometamol can increase plasma urea nitrogen and creatinine. As with other inhibitors of prostaglandin synthesis, it can be associated with adverse effects on the renal system, which can lead to glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome and acute renal failure.

Advanced renal diseases:
There is no information obtained from controlled studies on the use of dexketoprofen trometamol in patients with advanced renal disease. Therefore, ASEKET treatment is not recommended in patients with advanced renal disease. If ASEKET therapy is initiated, it is recommended to monitor the patient's kidney function closely.
Like all other NSAIDs, it can cause temporary small increases in some liver parameters and significant increases in SGOT and SGPT. Treatment should be terminated if there are any associated increases in such parameters.
Dexketoprofen should be used with caution in patients with hematopoietic disorders, systemic lupus erythematosus or mixed connective tissue disease.
Like other NSAIDs, dexketoprofen can also mask infectious diseases.

Cardiovascular thrombotic events:
Increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal were observed in clinical trials up to 3 years, made with a large number of selective and non-selective COX-2 inhibitors. All COX-2 selective and non-selective NSAIDs may carry similar risk. Patients with cardiovascular disease or known to carry a cardiovascular disease risk may be at a higher risk.
The lowest effective dose should be used along with possible minimum time to reduce the likelihood of a risk of adverse cardiovascular events in patients treated with nonsteroidal anti-inflammatory drugs. Even if there is no pre-existing cardiovascular symptom, the physician and the patient should be alert to such event developments. The patient should be informed about the symptoms and / or symptoms of serious cardiovascular events and what to do if they occur.

There is no consistent evidence that concurrent use of acetylsalicylic acid reduces the risk of increased cardiovascular thrombotic events associated with the use of NSAIDs.

Simultaneous use of nonsteroidal anti-inflammatory drugs with acetylsalicylic acid increases the risk of serious MI events (see section 4.4 Special warnings and precautions for use).

Two large, controlled clinical trials on COX-2 selective NSAIDs for pain treatment during the first 10-14 days following coronary artery bypass graft surgery showed an increase in the incidence of myocardial infarction and stroke (see section 4.3 Contraindications).

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with dexketoprofen after careful consideration.
Treatment should be initiated after careful consideration of the risk factors for cardiovascular disease (e.g., hypertension, hyperlipidemia, diabetes mellitus, and smoking) before beginning long-term treatment of patients.

Hypertension:
As in all other NSAIDs, dexketoprofen trometamol may cause hypertension or worsening of pre-existing hypertension, both of which may increase the risk of cardiovascular events. Diuretic treatment responses may be impaired when the thiazide group uses NSAIDs in patients treated with diuretics or loop diuretics. NSAIDs, including dexketoprofen trometamol, should be used with caution in hypertensive patients. The blood pressure should be closely monitored at the beginning of ASEKET treatment and during the course of treatment.

Skin reactions:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. ASEKET should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Anaphylactic reactions:
As with other NSAIDs, allergic reactions, including anaphylactic / anaphylactoid reactions, may occur with dexketoprofen in rare cases, without previous exposure. ASEKET should not be given to the patients with aspirin triad disease. This symptom complex typically occurs in asthmatic patients with nasal polyp or polyunsaturated rhinitis or bronchospasm with severe or fatal bronchospasm following the use of acetylsalicylic acid or NSAIDs (see section 4.3 Contraindications and section 4.4 Special warnings and precautions - pre-existing asthma). When an anaphylactoid reaction is observed, emergency services should be called.

Pregnancy:
Dexketoproden trometamol, like other NSAIDs, should not be used in late period of pregnancy because it may cause premature occlusion of the ductus arteriosus (clearance between the two large arteries [the aorta and the pulmonary artery], which is open in the womb of the mother and needs to close following birth, from the heart).

Like other NSAIDs, dexketoprofen trometamol may also damage female reproductive function and is not recommended for women who are considering to become pregnant. Treatment with dexketoprofen trometamol should be paused in patients having problem to become pregnant or having the infertility treatment.

Congestive heart failure and edema:
In some patients treated with NSAIDs, including dexketoprofen trometamol, fluid retention and edema were observed. Therefore, ASEKET should be used with caution in patients with fluid retention or heart failure.
Clinical trials and epidemiological data suggest that the use of certain NSAIDs (especially at high doses and in long-term therapy) may be associated with minor increases in risk of arterial thrombotic events (such as myocardial infarction or stroke). There is insufficient data to show that dexkotoprofen trometamol does not carry this risk.

Precautions:
General:
It shouldn't be expected that dexkeoprofen trometamol is replaced with corticosteroids or treated the corticosteroid deficiencies. Discontinuation of corticosteroids may cause the disease to exacerbate. Patients who are treated with long-term corticosteroid therapy, in case of discontinuation of corticosteroid therapy, their treatment should be decreased slowly and gradually.
The pharmacological activity of dexketoprofen trometamol in ASEKET [fever and] in reducing the inflammation may decrease the usefulness of these diagnostic indications used to diagnose complications of painful conditions thought to be infectious.

Hepatic effects:
Up to 15% of patients receiving NSAIDs, including dexketoprofen trometamol, may progress to borderline elevations in one or more liver tests. These laboratory anomalies may progress, remain unchanged, or go through automatically when treatment is continued. Significant increases in ALT and AST levels (three times or more the upper limit of the normal level) have been reported in approximately 1% of patients in clinical trials conducted with nonsteroidal anti-inflammatory drugs. In addition, rare cases of severe hepatic reactions have been reported, such as jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of which have also resulted in death. During long-term treatment with dexketoprofen trometamol, liver function should be monitored regularly as a precautionary measure. If abnormal liver function tests persist or worsen, appropriate clinical signs or symptoms develop in the liver disease or if other symptoms (e.g. eosinophilia, skin rashes, etc.) are seen the treatment with ASEKET should be discontinued.

Hematological effects:
Anemia is sometimes observed in patients receiving NSAIDs, including dexketoprofen trometamol. This may be due to fluid retention, GI blood loss or an undefined effect on erythropoiesis. Patients who have been treated for a long time with NSAIDs, including ASEKET, should regularly control their hemoglobin and hematocrit levels even if they do not show signs or symptoms of any anemia.
It was shown that nonsteroidal anti-inflammatory drugs prolongs the duration of bleeding that inhibits platelet aggregation in some patients. In contrast to acetylsalicylic acid, their effects on platelet function are less in point of qualitatively view, shorter-term, and reversible. Patients who have previously had coagulation disorders or have used anticoagulants and who may be adversely affected by platelet function changes should be carefully monitored during ASEKET use.

Pre-existing asthma:
Asthmatic patients may have acetylsalicylic acid-sensitive asthma. Acetylsalicylic acid use in acetylsalicylic acid-sensitive asthmatic patients has been associated with severe

bronchospasm, which can result in death. In the patients with hypersensitivity to acetylsalicylic acid, a cross reactiveness including bronchospasm was reported for using acetylsalicylic acid with NSAIDs together. ASEKET should not be used by the patients with hypersensitivity to this form of acetylsalicylic acid and should be used cautiously in patients with pre-existing asthma.

Laboratory tests:
Physicians should monitor patients for symptoms or symptoms of GI bleeding, since serious GI system ulcerations and bleeding may occur without stimulating symptoms. Full blood counts and biochemical profiles of patients with long-term NSAID therapy should be controlled periodically.

If clinical signs and symptoms consistent with liver or renal disease develop, or if systemic symptoms (eg eosinophilia, rash, etc.) arise, or if the liver test results are abnormal or worsen, ASEKET should be discontinued.

Paracetamol
In patients who use paracetamol for the first time or have a history of previous use, redness, rash or a skin reaction may occur at the first dose or repeated doses. In this case, the doctor should be contacted and the use of the drug should be discontinued and an alternative treatment should be initiated. The person who has a skin reaction with paracetamol should not use this medication or any other medication containing paracetamol. This can cause severe and fatal skin reactions including Steven Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP).

It should be used with caution under doctor's supervision in patients with anemia, lung disease, liver and kidney dysfunction. Patients with pre-existing hepatic disease may need to perform liver function tests at periodic intervals during high-dose or long-term treatment. In the event of renal insufficiency (creatinine clearance <10 ml / min), the physician must carefully evaluate the benefit / risk ratio of paracetamol use. Dose adjustment should be done and the patient should be monitored continuously.

The use of the drug should be re-evaluated in the following cases:
- If the medication is taken for pain (including rheumatoid pain): If adults do not get through the pain within 10 days, in children within 5 days, when the disease gets worse, when new symptoms occur or when the painful area swells with redness,
- If the medication is taken for fever: If the fever continues longer than 3 days, if the disease becomes worse or new symptoms arise,
- If the medication is taken for pharyngitis (sore throat): If pharyngitisis not treated within 2 days or if there is fever, headache, skin rash, nausea and vomiting.
Acute high doses of paracetamol may cause serious liver toxicity. Because of the risk of hepatotoxicity, paracetamol should not be taken at higher doses than recommended or longer. Patients with hepatic insufficiency (Child-Pugh category <9) should use paracetamol carefully.
For adults, the minimum toxic dose for a single intake is 7.5-10 grams, and for children 150 mg / kg.

If risk factors are present, doses below these may also have hepatotoxic effects. Risk factors include:

- If hepatic enzyme (CYP2E1) inductors are used: Carbamazepine, phenytoin, barbiturates, primidone, rifampin.
- If hepatotoxic drugs are used: Macrolides, anabolics, statins, ethionamide, niacin, isoniazid, phenothiazines.
- States of reduced glutathione reserves: Malnutrition, starvation, cachexia, HIV infection, and cystic fibrosis.

Laboratory test interactions:
In patients taking Paracetamol:

- Blood sugar: It is lower than that measured by glucose oxidase / peroxidase method. Hexokinase / glucose-6-phosphate appears to be the same as measured by dehydrogenase method.

- Uric acid in serum: It looks higher than it is when measured by phosphotungstate method.

- Bentiromide test results are invalid. Both paracetamol and bentiromide affect the amount of p-aminobenzoic acid by metabolized to an arylamine compound.

- Qualitative 6-hydroxyindole acetic acid (5 QAA) test in urine made with nitrosonaphthol reagent show fake positive. The quantitative test is not affected.

Taking concurrent paracetamol with moderate alcohol may lead to an increased risk of liver toxicity.

The daily dose of paracetamol should not exceed 2000 mg due to the risk of hepatotoxicity in alcohol user.

Acute high dose causes serious liver toxicity.

In adults, chronic daily doses may cause liver damage.

It should be used with caution in alcoholic liver patients.

4.5. Interaction with other medicinal products and other forms of interaction
Dexketoprofen
Combinations not recommended:
Other NSAIDs, including high doses of salicylates (≥ 3 g/day): administration of several NSAIDs together may increase the risk of gastrointestinal ulcers and bleeding, via a synergistic effect.

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4), due to the high plasma protein binding of dexketoprofen and the inhibition of platelet function and damage to the gastroduodenal mucosa. If the combination cannot be avoided, close clinical observation and monitoring of laboratory values should be carried out.

Warfarin: The effect of warfarin and NSAIDs on GI bleeding is synergistic; that is, patients taking these two drugs together are at greater risk of severe GI bleeding than patients taking these two drugs alone.

Heparins: increased risk of hemorrhage (due to the inhibition of platelet function and damage to the gastroduodenal mucosa). If the combination therapy cannot be avoided, close clinical observation and monitoring of laboratory values should be carried out.

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

Lithium (described with several NSAIDs): Nonsteroidal anti-inflammatory drugs lead to an increase in plasma lithium levels and a decrease in renal lithium clearance. The mean minimum lithium concentration increased by 15% and renal clearance decreased by approximately 20%. These effects are attributed to inhibition of renal prostaglandin synthesis by NSAID. Nonsteroidal anti-inflammatory drugs can reach toxic values that increase blood lithium levels (renal excretion of lithium is reduced). This parameter therefore requires monitoring during the initiation, adjustment and withdrawal of treatment with dexketoprofen.

Methotrexate (15 mg or more weekly): Nonsteroidal anti-inflammatory drugs have been reported to inhibit methotrexate accumulation in rabbit kidney sections on a competitive basis. This indicates that these may increase methotrexate toxicity. Caution should be exercised if nonsteroidal anti-inflammatory drugs are used concomitantly with methotrexate.

Hydantoines and sulphonamides: the toxic effects of these substances may be increased.

Acetylsalicylic acid: When dexketoprofen is given in combination with acetylsalicylic acid, protein binding rate is reduced even though free dexketoprofen clearance does not change. Although the importance of this interaction is clinically unknown, and concurrent administration of dexketoprofen and acetylsalicylic acid, as it is in other NSAIDs, is generally not recommended since it increases the possibility to occur of adverse effects.

Combinations requiring precautions:
Diuretics, ACE inhibitors, antibacterial aminoglycosides and angiotensin II receptor antagonists: Dexketoprofen may reduce the effect of diuretics and antihypertensive drugs. In some patients with compromised renal function (e. g. dehydrated patients or elderly patients with compromised renal function), the co-administration of agents that inhibit cyclooxygenase and ACE inhibitors, angiotensin II receptor antagonists or antibacterial aminoglycosides may result in further deterioration of renal function, which is usually reversible.

In case of combined prescription of dexketoprofen and a diuretic, it is essential to ensure that the patient is adequately hydrated and to monitor renal function at the start of the treatment (see section 4.4 Special warnings and special precautions for use).

Methotrexate, used at low doses, less than 15 mg/week: Hematological toxicity of methotrexate increased with anti-inflammatory agents decreasing renal clearance. Blood counts should be performed weekly during the first weeks of the combination. As in the elderly, it should be monitored more frequently in patients with mild renal dysfunction.

Pentoxyfilline: increased risk of bleeding. The patient should be monitored and followed more frequently in terms of bleeding time.

Zidovudine: Risk of increased red cell toxicity due to effect on reticulocytes with severe anemia occurring one week after ingestion of nonsteroidal anti-inflammatory drugs (reticulocyte release, an immature form of erythrocytes from bone marrow, increases with anemia). Blood levels should be monitored two weeks after treatment with nonsteroidal anti-inflammatory drugs.

Sulfonylureas: NSAIDs can increase the hypoglycemic effect of sulfonylureas by displacement from plasma protein binding sites.

Combinations needing to be taken into account:
Beta blockers: treatment with a NSAID may decrease their antihypertensive effect via inhibition of prostaglandin synthesis.

Cyclosporine and tacrolimus: Nonsteroidal anti-inflammatory drugs may increase the nephrotoxicity of cyclosporine and tacrolimus due to their effects with inhibition of renal prostaglandin synthesis. Renal functions should be measured during treatment.

Thrombolytics: increased risk of bleeding.

Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.

Probenecid: plasma concentrations of dexketoprofen may be increased; this interaction can be due to an inhibitory mechanism at the site of renal tubular secretion and of glucuronide conjugation and requires adjustment of the dose of dexketoprofen.

Cardiac glycosides: NSAIDS may increase plasma glycoside concentration.

Mifepristone: NSAIDS should not be used for 8-12 days after mifepristone administration.

Quinolone antibiotics: Animal studies show that high doses of quinolone in combination with NSAIDs may increase the risk of developing convulsions.

Furosemide: Clinical trials and post marketing observations show that dexketoprofen usage may reduce the natriuretic effect of furosemide and thiazides in some patients. This response is linked to the inhibition of renal prostaglandin synthesis. When co-administered with nonsteroidal anti-inflammatory drugs, the patient should be closely monitored for renal insufficiency (see section 4.4 Special use warnings and precautions - Renal effects) and diuretic efficacy.

Paracetamol
Drug interactions:
- Hepatic enzyme inducers (carbamazepine, phenytoin, barbiturates, primidone, rifampicin) accelerate the metabolism of paracetamol via CYP 2E1, reducing its clinical efficacy and accelerating the formation of toxic intermediates (NAPQI).
- The risk of hepatotoxicity of paracetamol is risen in those who uses hepatotoxic drugs (macrolides, anabolics, statins, ethionamide, niacin, isoniazid, phenothiazines).
- The use of high doses of paracetamol together with warfarin, kumarin and indandion class anticoagulants increases anticoagulant efficacy. In this case, prothrombin time definitions should be performed frequently and anticoagulant doses should be adjusted if necessary. However, if paracetamol is used for a short time in normal dosage and is used chronically less than 2 grams per day, this is not necessary.
- Long-term use of salicylate and paracetamol combinations increases the risk of analgesic nephropathy. When used in such high doses (1.35 grams per day or cumulatively 1 kg per year) and for long periods (3 years or more), the risk of analgesic nephropathy, renal papilla

necrosis, terminal renal failure and renal or bladder cancer increases. The dose of combination must not exceed the individual doses of salicylate or paracetamol.

For possible combination doses:
- Long-term use of paracetamol with nonsteroidal anti-inflammatory drugs increases the risk of adverse renal effects. Such combinations should be used under the supervision of a doctor.
- Diflunisal increases plasma concentrations of paracetamol by 50% and increases the risk of hepatotoxicity.
- When paracetamol is given with probenecid, the plasma clearance of paracetamol is reduced, the half-life prolongs. The elimination of paracetamol, glucuronide and sulfate conjugates is reduced.
- If cholestyramine is given within one hour after the administration of paracetamol, the absorption of paracetamol is reduced.
- Metoclopramide and domperidone type gastrokinetic drugs increase paracetamol absorption. However, there is no need to avoid using it together.

Interactions with food:
- The risk of hepatotoxicity of paracetamol increases in acute toxic doses or in chronic high doses in those who regularly drink harmful amounts of alcohol. These patients should use another analgesic instead of paracetamol.
- Absorption slows down if paracetamol is taken after a meal containing high carbohydrates. However, the amount entering the systemic circulation does not change. In vegetarians paracetamol absorption slows down and decreases.

Biological interactions:
- Paracetamol does not diminish the immunostimulant effect of vaccines when used with the aim of treating and preventing vaccine reactions such as pain and fever. However, DTaP (diphtheria-tetanus toxoids-acellular pertussis) is ineffective in preventing the reactions of the vaccine.

Interactions with herbal products:
- Hibiscus has been reported to reduce plasma concentrations of paracetamol. The clinical significance of this is unknown.
- The risk of hepatotoxicity may increase when paracetamol is taken with hepatotoxic potential plant products such as echinacea (Echinacea augustifolia), kava (Piper methysticum) and salicylate willow (Salix alba) and meadow horn (Spiraea ulmaria).
- The risk of bleeding may increase when used in combination with paracetamol antithrombotic agents gingko (gingko biloba), ginseng (Panax ginseng), garlic (Allium sativum), blueberries (Vaccinium myrtillis), chrysanthemum parthenium
- The risk of bleeding may increase when paracetamol is used in combination with gum arabic (Anthemis nobilis), horse chestnut (Aesculus hippocastaneum), cedar grass (Trigonella foenum graecum), red clover (Trifolium pratense) and tamarind (Tamarindus indicus).
- Mary's main stand (Silybum marianum): Cilimarin prepared from this plant, is a mixture of complex flavonoids. Experimentally, it increases liver glutathione levels in rats.

Additional information for special populations
No interaction studies have been done on specific populations.

Pediatric population:
No interaction studies of the pediatric population have been conducted.

4.6. Fertility, pregnancy and lactation
General advise:
Pregnancy category: C

Women of childbearing potential/Birth control (contraception)
Like other NSAIDs, dexketoprofen trometamol, one of the active ingredients of ASEKET, can impair female reproductive function and is not recommended for use in women who are considering pregnancy. Dexketoprofen trometamol treatment should be discontinued in patients who have trouble getting pregnant or infertility treatment. There is no data on the effect of ASEKET on birth control.

Pregnancy
Studies on animals are insufficient in terms of effects on pregnancy / and / or / embryonal / fetal development / and / or / and / or postnatal development (see section 5.3). The potential risk for humans is unknown.

ASEKET should not be used during pregnancy unless necessary.

Dexketoprofen
Inhibition of prostaglandin synthesis may affect pregnancy and / or embryo / fetal development. The data obtained from epidemiology studies showed that after using prostaglandin synthesis inhibitor in the early stages of pregnancy, there was an increase in the risk of gastro-schizis and cardiac malformation and abortion. The risk of cardiac malformation increased from 1% to approximately 1.5%. Risk is believed to increase with dose and duration of treatment. Studies in animals have shown that the use of prostaglandin synthesis inhibitor leads to increased pre- and post-implantation loss and embryo-fetal death. The prostaglandin synthesis inhibitor administered to animals in the organogenic process has increased the incidence of various malformations including cardiovascular. Reproductive toxicity was not observed in animal studies conducted with dexketoprofen trometamol. Dexketoprofen trometamol should not be administered unless necessary during the first and second trimesters of pregnancy. If dexketoprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to;
• cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
• renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy, to:
• possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
• inhibition of uterine contractions resulting in delayed or prolonged labour.

Paracetamol
When given to the mother at therapeutic doses, paracetamol passes through the placenta within 30 minutes at the earliest. In paralysis, paracetamol is effectively metabolized by sulfate conjugation.

Breast-feeding
It is not known whether Dexketoprofen has passed through the breast milk. Although paracetamol is excreted in breast milk, there is no evidence that it is contraindicated in breastfeeders. However, it is not recommended to use in lactation due to dexketoprofen content in ASEKET.

Fertility
No effect on fertility has been reported. Reproductive toxicity was not observed in animal studies carried out with dexketoprofen trometamol.
Chronic toxicity studies in animals have reported that paracetamol was caused by testicular atrophy and inhibited spermatogenesis. There are no studies on fertility in humans.

4.7. Effects on ability to drive and use machines
ASEKET may cause dizziness and drowsiness, which may have mild or moderate effects on the ability to drive or use machines. Care must be taken or avoided when using machines or driving.

4.8. Undesirable effects
The frequency of side effects reported with the use of dexketoprofen and paracetamol in ASEKET content is as follows:
(very common (≥ 1/10); common (≥ 1/100 to< 1/10); not common (≥ 1/1.000 to < 1/100); rare (≥ 1/10.000 to < 1/1.000); very rare (< 1/10.000), not known (can not be estimated based on available data).

Dexketoprofen
Blood and lymphatic system disorders:
Very rare: Neutropenia, thrombocytopenia

Immune system disorders:
Very rare: Anaphylactic reaction including anaphylactic shock

Metabolism and Nutrition disorders
Rare: Anorexia

Psychiatric disorders
Not common: Anxiety, insomnia

Nervous system disorders:
Not common: Headache, dizziness, somnolence
Rare: Paresthesia, syncope

Eye disorders
Very rare: Blurred vision

Ear and labyrinth disorders
Not common: Vertigo
Very rare: Tinnitus

Cardiac disorders
Not common: Palpitation
Very rare: Tachycardia

Vascular disorders
Not common: Flushing
Rare: Hypertension
Very rare**:** Hypotension

Respiratory, thoracic and mediastinal disorders
Rare: Bradypnoea
Very rare: Bronchospasm, dyspnea

Gastrointestinal disorders
Common: Nausea and/or vomit, abdominal pain, diarrhea, dyspepsia
Not common: Gastritis, constipation, dry mouth, flatulence
Rare**:** Peptic ulcer, peptic ulcer hemorrhage or peptic ulcer perforation
Very rare: Pancreatitis

Hepato-biliary disorders
Very rare: Hepatocellular injury

Skin and subcutaneous tissue disorders
Not common: Rash
Rare: Acne, increase in sweating, urticaria
Very rare: Stevens Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), angioneurotic edema, facial edema, photosensitivity reactions, pruritus

Musculoskeletal and connective tissue disorders
Rare: Back pain

Renal and urinary tract disorders
Rare: Polyuria
Very rare: Nephritis or nephrotic syndrome

Reproductive system and breast disorders
Rare: Menstrual disorder, prostatic disorder

General disorders and administration site conditions:
Not common: Fatigue, pain, asthenia, trembling, malaise
Rare: Peripheral edema

Investigations:
Rare: Liver function test abnormality

Gastrointestinal: In general, the most common side effects are GI disorders. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur. Following administration, vomiting, nausea, diarrhea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, colitis exacerbation and Crohn's disease were reported. Gastritis was observed in less frequency.

Edema, hypertension and cardiac failure have been reported in association with nonsteroidal anti-inflammatory drug therapy.

The adverse effects observed in other NSAIDs may also be observed with dexketoprofen; aseptic meningitis (more common in people with lupus erythematosus or mixed connective tissue disease); hematologic reactions (purpura, aplastic and hemolytic anemia, and rarely agranulocytosis and medullary hypoplasia).
Stevens Johnson syndrome and bullous reactions including toxic epidermal necrosis (very rare).

Clinical trials and epidemiological data suggest that small increases in the risk of developing arterial thrombotic events (myocardial infarction or heart attack) may be associated with the use of certain NSAIDs (especially high doses and long-term therapy) (see section 4.4 Special precautions and warnings).

Paracetamol
Paracetamol is widely used, and when taken at the recommended doses, side effects are mild and generally occur rarely.

Infections and infestations
Common: Infection

Blood and lymphatic system disorders
Very rare: Agranulocytosis, thrombocytopenia, (isolated notifications)

Immune system disorders
Rare: Eruption, urticaria
Very rare: Lyell syndrome, Stevens Johnson syndrome (isolated notifications)
Not known: Bronchospasm*, anaphylactic shock, positive allergy test**, immune thrombocytopenia ***

Metabolism and nutrition disorders
Rare: Hypoglycemia

Nervous system disorders
Common: Headache, dizziness, drowsiness, paresthesia

Ear and labyrinth disorders
Not common: Balance disorder

Cardiac disorders
Rare: Arrhythmia

Vascular disorders
Very rare: Purpura

Respiratory, thoracic and mediastinal disorders
Common: Upper respiratory tract infection

Gastrointestinal disorders
Common: Nausea, diarrhea, dyspepsia, flatulence, abdominal pain, constipation, vomiting
Not common: Gastrointestinal bleeding

Hepato-biliary disorders
Very common: ALT above upper limit
Common: ALT 1.5 fold of upper limit

Skin and subcutaneous disorders
Rare: Skin rash, pruritus, urticaria, allergic edema and angioedema, acute generalized exanthematous pustulosis, erythema multiform, Stevens-Johnson syndrome and toxic epidermal necrolysis (including fatal outcomes)

Renal and urinary disorders
Rare: Diuresis

General disorders and administration site conditions
Common: Face edema
Not common: Peripheral edema
Very rare: Fever, asthenia

Surgery and medicinal procedures
Not common: Post-tonsillectomy bleeding
Common: Post-extraction (third molar tooth) bleeding

In a second literature review involving 2100 patients with paracetamol and NSAIDs, treatment discontinuation was more frequent due to the inadequacy of the drug effect in the paracetamol group. One out of every 10 patients who received paracetamol treatment discontinued treatment, and one out of every 15 patients discontinued treatment because it found the efficacy of the drug to be insufficient. Compared with nonsteroidal anti-inflammatory drugs, the rate of discontinuation due to side effects is lower.
Clinical laboratory assessments showed that the side effects of paracetamol used in therapeutic doses in clinical trials and the changes in laboratory values were not different from those of placebo. Changes in biochemical values related to liver function indicate that the drug is taken at toxic doses. If the drug is taken at toxic doses, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) begin to rise within 24 hours and reach the peak after 72 hours. Elevation of any of these above 1000 units is descriptive for hepatotoxicity. Besides that, bilirubin and creatinine are elevated and glucose is decreased. Arterial pH drops below 7.30, creatinine increases above 3.4 mg / dL, prothrombin time exceeds 100 seconds, and serum lactate levels rise above 3.5 mmol / L, suggesting that the prognosis is not good. Reliability in specific groups and situations are internal and external factors. Differences in gender, race, height, weight, body structure, lifestyle, and susceptibility to paracetamol have not been reported in response to undesired and toxic effects of paracetamol. Apart from these, risk factors that increase susceptibility to the toxic effects of paracetamol are part of drug interactions. (See section 4.5.) Children younger than 6 years are less susceptible to toxic effects of paracetamol. It has been suggested that the glutathione reservoirs and detoxification rate are high.

*Bronchospasm: It is seen in 20% of patients with acetylsalicylic acid- sensitive asthma.
** Oral provocation test with paracetamol: It is positive in 15.5% of patients with paracetamol-related allergic symptoms (eruption, urticaria, anaphylaxis).
***Immune thrombocytopenia: In the presence of paracetamol and paracetamol sulphate, antibodies bind to GPIIb / IIIa and GPIb / IX / V receptors of platelets. A literature review of 2000 patients comparing paracetamol with placebo and NSAIDs showed no difference in the frequency of side effects and discontinuation between paracetamol and placebo after discontinuation of paracetamol treatment.

4.9. Overdose and treatment

Dexketoprofen

If dexketoprofen is accidentally or excessively taken, symptomatic treatment should be applied immediately according to the clinical condition of the patient. Symptoms following overdose are not known. Similar medicinal products have been reported to cause GI (vomiting, anorexia, abdominal pain) and neurological (drowsiness, dizziness, attention loss, headache) disorders. Activated charcoal should be administered if more than 5 mg/kg has been ingested by an adult or a child within an hour.

Dexketoprofen trometamol may be removed by dialysis.

Paracetamol

If you use more than 10 g in adults, there is a possibility of toxicity. Moreover, overdose damage is greater in people with non-cirrhotic alcoholic liver disease. Liver damage following overdose in children is relatively rare.

With paracetamol overdose with liver cell damage, the paracetamol half-life, which is around 2 hours in normal adults, usually lasts for 4 hours or longer. Reduction in $^{14}CO_2$ elimination after ^{14}C-aminopyridine has been reported. This shows better the relationship between paracetamol overdose and liver cell damage compared to plasma paracetamol concentration or half-life or conventional liver function test measurements.

Renal failure may occur due to acute tubular necrosis following fulminant hepatic failure due to paracetamol. However, this group is not frequent in patients when compared with patients with fulminant hepatic failure due to other reasons for the incidence. Rarely, renal tubular necrosis can occur only after minimal hepatic toxicity, 2-10 days after taking the drug. It has been reported that chronic alcohol intake in a patient who received an overdose of paracetamol contributed to the development of acute pancreatitis. In addition to acute overdose, liver damage and nephrotoxic effects have been reported after excessive daily intake of paracetamol.

Symptom and indications:

Paleness, anorexia, nausea and vomiting are common early symptoms of paracetamol overdose. Hepatic necrosis is a dose related complication of paracetamol overdose. Hepatic enzymes can rise and prothrombin time is prolonged within 12 to 48 hours, but clinical symptoms may not be apparent within 1 to 6 days of drug ingestion.

Treatment:

The paracetamol overdose should be treated immediately to protect the patient against delayed hepatotoxicity. For this, it is necessary to reduce absorption (gastric lavage or activated charcoal) followed by intravenous N-acetylcysteine or oral methionine. Methionine should not be used if the patient is vomiting or conjugated with activated charcoal. Peak plasma paracetamol concentrations may be delayed up to 4 hours following hyperemesis. For this reason, plasma paracetamol levels should be measured at least 4 hours after drug ingestion to determine the risk of hepatotoxicity. Additional treatment (supplemental oral methionine or intravenous N-acetylcysteine) should be considered under the light of the blood paracetamol content and time since drug ingestion. Patients taking hepatic enzyme-inducing drugs are advised to reduce the therapeutic dose of N-acetylcysteine by 30-50% in patients with long-lasting alcohol dependence or chronic nutritional deficiencies, because these patients may be more susceptible to the toxic effects of paracetamol. Treatment of fulminant hepatic insufficiency that may develop following paracetamol overdose requires specialization.

5. PHARMACOLOGICAL PROPERTIES

5.l. Pharmacological properties

Pharmacotherapeutic group: Propionic acid derivatives, analgesic and antipyretics
ATC code: M01AE17 (dexketoprofen) and N02BE01 (paracetamol)

Dexketoprofen trometamol

Dexketoprofen trometamol is a salt of S - (+) - 2- (3-benzoylphenyl), analgesic, anti-inflammatory and antipyretic drug in NSAID group.

The mechanism of action of nonsteroidal anti-inflammatory drugs relates to the reduction of prostaglandin synthesis by the inhibition of the cyclooxygenase pathway. In particular, prostaglandins occur by the inhibition of cyclic endoperoxides, PGG2 and PGH2, of arachidonic acid, which form PGE1, PGE2, PGF2a, and PGD2 and also prostacyclin PGI2 and thromboxanes (TXA2 and TXB2). In addition, the inhibition of prostaglandin synthesis also affects other inflammatory mediators, such as quinine, leading to an indirect effect in addition to direct effect. Dexketoprofen inhibits prostaglandin synthesis centrally and peripherally.

Studies conducted on experimental animals and humans have demonstrated that dexketoprofen is an inhibitor of COX-1 and COX-2 activities.

Clinical trials in various pain models have shown that dexketoprofen trometamol is an effective analgesic effect. In some studies, the analgesic effect started within 30 minutes after administration of dexketoprofen. Analgesic effect lasts 4-6 hours.

Paracetamol

Paracetamol is an analgesic and antipyretic drug. This effect is due to inhibition of prostaglandin synthesis in the central nervous system and peripherally. Prostaglandins increase the sensitivity of painful nerve endings.

Paracetamol inhibits the synthesis of prostaglandins, reducing the sensitivity of these nerve endings, raising the pain threshold, inhibiting the onset and communication of the stimuli. The antipyretic effect is due to the fact that the thermoregulation center in the anterior hypothalamus prevents prostaglandin E2 stimulation. The anti-inflammatory effect of paracetamol is minimal.

5.2. Pharmacokinetic properties

General characteristics

Dexketoprofen

Absorption:

After oral administration of dexketoprofen trometamol to humans, the Cmax is reached at 30 min (range 15 to 60 min).

When administered concomitantly with food, the AUC does not change, however the Cmax of dexketoprofen trometamol decreases and its absorption rate is delayed (increased tmax).

Distribution:

The distribution half-life of dexketoprofen trometamol is 0.35 hours. Dexketoprofen binds to plasma proteins, particularly albumin (99%), as in other drugs, the mean value of the dispersion volume is less than 0.25 L / kg. In multidose pharmacokinetic studies, the observation that AUC after the last administration is not different from that obtained after a single dose is indicative of no drug accumulation. Dexketoprofen is not involved in the accumulation of xenobiotics in adipose tissues.

Elimination:
The main elimination route for dexketoprofen is glucuronide conjugation followed by renal excretion. After administration of dexketoprofen trometamol only the S(+) enantiomer is obtained in urine, demonstrating that no conversion to the R-(-)enantiomer occurs in humans. Elimination of half life of dexketoprofen trometamol is 1.65 hours.

Linearity/Non-linearity:
The pharmacokinetic parameters obtained after repeated dosing with dexketoprofen trometamol are similar to those showing no drug accumulation after single dose administration.

Paracetamol

Absorption:
When paracetamol is taken orally, its absorption is rapid and complete. If taken after a meal containing high carbohydrate, absorption is reduced. In the case of fasting condition, the absolute bioavailability is 62% -69%. This reduction in bioavailability is due to the first pass metabolism of approximately 20% of the oral dose given. Peak plasma concentrations reach 0.5-2 hours. After oral doses up to 650 mg, plasma peak concentrations are 5-20 μg / ml (33.1- 132.4 mmol / L). The analgesic effect begins at 30 minutes, reaches a maximum of 1-3 hours and lasts 3-4 hours.

Distribution:
Paracetamol is widely distributed in body tissues and fluids. It passes through breast milk. After 1-2 hours form the administration of 650 mg dose by the mother, the concentrations in breast milk are 10-15 μg / ml (66,2-99,3 mmol / L). The mean milk / plasma concentration ratio is 1.24. Protein binding rate is low and is between 20-50%. The volume of distribution is 0.95 L / kg.

Biotransformation:
90-95% of an oral dose given is metabolized in the liver by conjugation with glucuronic acid, sulfuric acid and cysteine. 5% less urine eliminated as unchanged in the urine. A small amount of paracetamol is converted to N-acetyl-para benzoquinoneimine (NAPQI) by N-hydroxylation by cytochrome P450 mixed-function oxidase enzymes (mainly CYP2E1, less CYP1A2 and CYP3A4) in liver microsomes. This metabolite is highly reactive and normally combines with glutathione via the glutathione synthase enzyme, and this complex is excreted in the form of cysteine and mercapturic acid conjugates. However, if paracetamol is taken in high amounts, this mechanism is saturated and reacts with sulfhydryl groups of metabolite liver proteins, causing hepatic necrosis.

Elimination:
Paracetamol is renally excreted in the form of metabolites. Half life is 1-4 h (mean 2.7 h), renal clearance is 5 ml / min. In acute overdose, this time may be prolonged in liver disease, newborn, elderly; in the population of children it is shorter. Paracetamol can be removed by hemodialysis and hemoperfusion from the blood. Blood can be cleaned from paracetamol as hemodialysis can be performed at 120 ml / min, hemoperfusion at 200 ml / min, and peritoneal dialysis at <10 ml / min.

Linearity/Non-linearity:
In general, there is no correlation between serum concentrations of paracetamol and analgesic effect.

Characteristic properties in patients:
Dexketoprofen

Renal dysfunction:
After receiving a single dose of 12.5 mg dexketoprofen trometamol, volunteers with mild to moderate renal impairment showed an increase of only 22% and 37%, respectively, in C_{max} compared with healthy volunteers.

Liver dysfunction:
After receiving a single dose of 12.5 mg dexketoprofen trometamol, volunteers with mild to moderate renal impairment showed an increase of only 22% and 37%, respectively, in C_{max} compared with healthy volunteers.

Elders:
After oral administration of 25 mg of dexketoprofen trometamol, an increase of approximately 50% in the AUC and half-life values of elderly volunteers were observed when compared to young volunteers and a decrease of 40% was observed after single or repeated doses.

Paracetamol
Renal dysfunction:
In renal failure, paracetamol absorption is normal and terminal half-life is prolonged. In patients with moderate renal impairment, plasma concentrations of paracetamol glucuronide and sulphate conjugates are increased and plasma half-lives are prolonged (glucuronide 30.6 hours, sulphate 21.8 hours, normally 3 hours). Concentrations of these metabolites are even higher in dialysis patients. Concentrations of cysteine and mercapturic conjugates are extremely low. The ratios of paracetamol metabolites in patients with moderate renal insufficiency are the same in healthy subjects.

Liver diseases:
In liver diseases, the half-life of paracetamol is longer than in healthy individuals. Paracetamol bioavailability remains unchanged in patients with chronic non-alcoholic liver disease. It also does not aggravate the clinical manifestations and laboratory parameters of paracetamol disease given at therapeutic doses. Paracetamol is contraindicated in active liver disease, liver failure and chronic alcoholism.

Pediatric population:
The elimination half-life of paracetamol is shorter in children and in newborns. In prematurity, in newborns and in children up to 10-12 years of age, sulphate conjugation is mainly metabolic. Oxidative metabolism products (NAPQI) are not found in urine in children aged 3-9 years.

Geriatric population:
Absorption and distribution of paracetamol in elderly patients do not change in volume; half life and clearance can be reduced. However, these changes are not at a level that will require dose adjustment.

5.3. Preclinical safety data

Dexketoprofen

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and immunopharmacology. The chronic toxicity studies carried out in mice and monkeys gave a No Observed Adverse Effect Level (NOAEL) of 3 mg/kg/day. The main adverse effect observed at high doses was gastrointestinal erosions and ulcers that developed dose dependently.

Paracetamol

Chronic toxicity studies in experimental animals have reported that paracetamol caused testicular atrophy and inhibited spermatogenesis In humans, no controlled research has been done to examine the effect on pregnancy. Chronic daily paracetamol has been reported to cause "analgesic nephropathy", which can impair renal function. Paracetamol has hepatotoxic effects when the usual therapeutic doses are exceeded. An intermediate metabolite (N-acetyl-benzoquinoneimine), which has this effect and is formed in the liver, is normally neutralized by the sulfhydryl groups in glutathione. At high doses, the sulfhydryl groups in the resulting liver proteins that start to saturate this system begin to react and the liver becomes necrotic.

The LD50 value found in acute toxicity tests in mice is 610 mg / kg. When given in cats at a dose of 25 mg / kg and then 50 mg / kg for 22 weeks, it caused severe liver necrosis. Rats are less sensitive to the toxic effect of the drug. The reported LD50 for this species is 1000 mg/ kg and liver necrosis is not seen even at these doses. In addition, different LD50 values have been reported for the same species.

6. PHARMACEUTICAL PARTICULARS

6.l. List of excipients

Microcrystalline cellulose (E460)
Colloidal silicone dioxide
Pregelatinized starch
Sodium starch glycolate
Magnesium stearate
Partial hydrolyzed polyvinyl alcohol
Titanium dioxide (E 171)
Polyethylene glycol (macrogol)
Talc

6.2. Incompatibilities

There is not any known incompatibilities.

6.3. Shelf Life

24 months

6.4. Special precautions for storage

Store at room temperature under 25 °C and protect from light in the original package.

6.5. Nature and contents of container

The 20 film-coated tablets are packaged with transparent PVC/PVDC/Aluminum foil blister in carton box with instructions for use.

6.6. Special precautions for disposal and other handling

Unused product or waste materials should be disposed of according to the regulations on "Control of Medicinal Wastes" and "Control of Packaging and Packaging Wastes.

7. MARKETING AUTHORISATION HOLDER:

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