1 PRODUCT NAME

DISTEM 380 mg/300 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 380 mg of methocarbamol and 300 mg of paracetamol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

Round biconvex white tablets, scored on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders.

4.2 Posology and method of administration

Posology

Treatment with methocarbamol should be as short as possible. As soon as the pain dissapears, the administration should be discontinued.

Adults: 2 tablets every 4-6 hours (four to six times daily), depending on the severity of the symptoms. The maximum dose of 12 tablets in 24 hours should not be exceeded.

Patients with renal impairment
In patients with renal impairment the dose should be reduced depending on the glomerular filtration rate, according to the following table:

GLOMERULAR FILTRATION	DOSE
10-50 mL/min	1 tablet each 6 h
< 10 mL/min	1 tablet each 8 h

Patients with hepatic impairment
In case of hepatic impairment the dose of 2 g of paracetamol / 24 hours should not be exceeded (maximum 6 tablets/day divided in 3-6 doses) (see section 4.4).

Since the elimination half-life of methocarbamol may be higher in these patients, longer intervals between doses could be required.

Older People

In elderly patients an increase in the elimination half-life of paracetamol has been observed , being half of the dose of methocarbamol sufficient to obtain a therapeutic response. Therefore it is recommended to reduce the dose to 1 tablet every 4 hours or 2 tablets every 8 hours.

Method of administration:

The tablets can be swallowed with a little water.

4.3 Contraindications

- Known hypersensitivity to the active substances (methocarbamol, paracetamol) or to any of the excipients listed in section 6.1.
- Coma or precoma states.
- Known brain damage.
- History of seizures or epilepsy.
- Myasthenia gravis.

4.4 Special warnings and precautions for use

Concomitant use of more than one medicinal product containing paracetamol can lead to intoxication (see section 4.9). Patients should be warned of the risk of intoxication due to concomitant intake of more than one medicinal product containing paracetamol. Toxicity due to paracetamol can occur due to intake of a single overdose or due to accumulation after repeated intake of high doses of paracetamol (see section 4.9)

This medicinal product should be administered with caution, avoiding prolonged treatment in patients with glucose-6-phosphate dehydrogenase deficiency, anaemia, heart or lung disease.

The use in patients who regularly consume alcohol (three or more alcoholic drinks per day) may cause liver damage. Chronic alcoholics should not take more than 2 g of paracetamol per day (maximum 5 tablets daily). During treatment with paracetamol no alcohol should be taken.

In asthmatic patients sensitive to acetylsalicylic acid Caution is recommended because mild bronchospasm after intake of paracetamol (cross-reaction) has been reported (see section 4.8); although this has only been reported in a minority of these patients, it can lead to severe reactions, specially after intake of high doses.

Special populations:
Renal and hepatic impairment.
This medicine should be used with caution in patients with renal or hepatic impairment.

In patients with hepatic and renal insufficiency, methocarbamol should be used with caution, avoiding long-term treatments.

Patients with renal impairment should ask their doctor or pharmacist before taking this medicine since dose adjustment may be required (see section 4.2). In cases of severe renal impairment, occasional use of paracetamol is acceptable but prolonged administration of high doses may increase the risk of hepatic and renal adverse effects.

Caution is recommended for the administration of paracetamol to patients with mild to moderate hepatic impairment (including Gilbert's syndrome), severe hepatic impairment (Child-Pugh> 9), acute hepatitis, glutathione deficiency, dehydration, chronic malnutrition and history of alcohol abuse (see section 4.2) and concomitant treatment with hepatic enzyme inducers (see section 4.5).

Interference with diagnostic tests:

Paracetamol may interfere with the analytical determination of uric acid and glucose.

Methocarbamol may cause colour interference in some analytical tests such as 5-hydroxyindolacetic acid (5-HIAA) using nitrosoaphthol reagent and urinary vanillymandelic acid (VMA) determination, using the Gitlow method. In some patients a change in the colour of urine samples during storage, turning brown, black, blue or green, has also been reported

4.5 Interactions with other drugs and other forms of interaction

Methocarbamol:

Methocarbamol may increase the effects of other central nervous system depressants and stimulants, including alcohol, barbiturates, anaesthetics and appetite suppressants.

Methocarbamol may also potentiate the effects of anticholinergics, such as atropine, and some psychotropic drugs.

Methocarbamol may inhibit the effect of pyridostigmine bromide. Therefore, it should be used with caution in patients with myasthenia gravis treated with acetylcholinesterase inhibitors.

Paracetamol:

Paracetamol is metabolised in the liver, and the resulting hepatotoxic metabolites may interact with drug products that use the same metabolic routes. These drug products are:

- Oral anticoagulants (**acenocoumarol, warfarin**): Chronic administration of paracetamol at doses higher than 2 g/day with these medicinal products may increase their anticoagulant effect. This seems to be due to a decrease in vitamin K dependent coagulation factors by inhibition of enzymes involved in their hepatic synthesis. The interactions between paracetamol and oral anticoagulants may potentiate the anticoagulant effect increasing the risk of bleeding. Given the apparent limited clinical relevance at doses below 2 g/day paracetamol should be considered as therapeutic alternative to salicylate analgesics in patients treated with anticoagulants. However in these patients INR should be periodically controlled.
- Alcohol: Increase in paracetamol toxicity , possibly by inducing production of hepatotoxic metabolites in the liver.
- Anticholinergics (glycopyrronium, propantheline): decrease in rate of gastric emptying which leads to a reduction in paracetamol absorption, with possible decrease of its effect.
- Anticonvulsants (phenytoin, phenobarbital, methylphenobarbital, primidone): decrease in paracetamol bioavailability and increase of hepatotoxicity after overdose, due to induction of the hepatic metabolism.
- Loop diuretics: the effects of diuretics may be reduced as paracetamol may reduce renal excretion of prostaglandins and plasma renin activity.
- Isoniazid: reduction in paracetamol clearance, with possible potentiation of its effect and/or toxicity, by inhibiting its hepatic metabolism.
- Lamotrigine: decrease in bioavailability of lamotrigine, with possible reduction of its effect, due to possible induction of hepatic metabolism.
- Metoclopramide and domperidone: these drugs increase paracetamol absorption in the small intestine, due to their effect on gastric emptying and thus to a delay in the onset of the action.
- Probenecid: increases plasma half-life or paracetamol, by decreasing the degradation and urinary excretion of its metabolites.
- Propranolol: increase in paracetamol plasma levels, due to possible inhibition of its hepatic metabolism.
- Rifampicin: increase in paracetamol clearance and formation of hepatotoxic metabolites, due to a possible induction of the hepatic metabolism.

- Ion-exchange resins (cholestyramine): reduction of paracetamol absorption and possible inhibition of its effect, due to intestinal adhesion of paracetamol.
- Chloramphenicol: enhanced chloramphenicol toxicity, due to possible inhibition of its hepatic metabolism.
- Zidovudine (AZT): concomitant intake with paracetamol increases the risk of a reduction in white blood cells (neutropenia). Therefore, paracetamol should not be taken together with AZT, except after medical prescription.

4.6 Fertility, pregnancy and lactation

Pregnancy

Paracetamol crosses the placental barrier.

A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

No studies have been carried out with methocarbamol on animal reproduction. It is not known whether methocarbamol may damage the foetus or affect reproductive capacity when administered to pregnant women.

Safety of methocarbamol with regard to possible adverse effects on foetal development has not been established. Isolated cases of foetal and congenital abnormalities after intrauterine exposition to methocarbamol have been described.

Methocarbamol is not recommended for pregnant women or women planning to become pregnant, particularly in the early stages of pregnancy, unless the doctor considers that the potential benefits outweigh the possible risks.

Breast-feeding

Methocarbamol and/or its metabolites are excreted in animal milk (dogs). However, it is not known whether methocarbamol or its metabolites are excreted in human milk.

Paracetamol is excreted in human breast milk but not in a clinically significant amount.

Accordingly, caution should be taken when administering this medicine to breastfeeding women.

Fertility

Male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

This medicine may cause drowsiness. Accordingly, patients should not drive or operate machinery unless they are sure that their mental capabilities remain unaffected, especially if it is taken concomitantly with other drugs which may also cause drowsiness.

4.8 Undesirable effects

Summary of the safety profile

No serious adverse events have been reported in the clinical studies with the combination of paracetamol and methocarbamol published in literature.

The most frequent adverse reaction reported after methocarbamol is headache. The most frequently reported adverse reactions during the use of paracetamol are hepatotoxicity, renal toxicity, blood disorders, hypoglycaemia and allergic dermatitis.

Tabulated list of adverse reactions

The adverse reactions observed with the combination of paracetamol and methocarbamol are represented in the table below. They are listed by MedDRA system organ class (SOC) and frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (frequency cannot be estimated from available data).

System organ class	Frequency		
	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Unknown
Blood and lymphatic system disorders		Thrombocytopeniab, agranulocytosisb, leukopeniab, neutropeniab, pancytopeniab, haemolytic anaemiab	Leukopeniaa,
Immune system disorders		Anaphylactic reactiona, hypersensitivity reactions ranging from a simple skin eruption (rash) or urticaria to angioedema and anaphylactic shockb	
Metabolism and nutrition disorders		Hypoglycaemiab	
Psychiatric disorders		Nervousnessa, anxietya, confusiona	
Nervous system disorders	Headachea, dizziness (or light headedness)a	Syncopea, nystagmusa, tremora, seizures (including grand mal)a, somnolencea	Muscle incoordinationa, amnesiaa, insomniaa, vertigoa
Eye disorders	Conjunctivitisa	Blurred visiona	Diplopiaa

Cardiac disorders		Bradycardiaa	
Vascular disorders	Hypotensionc	Flushinga	
Respiratory, thoracic and mediastinal disorders	Nasal congestiona	Bronchospasmb	
Gastrointestinal disorders	Dysgeusia (metallic taste)a	Nauseaa, vomitinga	Dyspepsiaa, dry mouthа, diarrhoeac
Hepatobiliary disorders	Increased hepatic transaminase levelsb	Hepatotoxicity (jaundice)b	Jaundice (including cholestatic jaundice)a
Skin and subcutaneous tissue disorders	Angioedemaa, pruritusa, rasha, urticariaa	Allergic dermatitisb, severe skin reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis)b	
Renal and urinary disorders		Sterile pyuria (cloudy urine)b, adverse renal disordersb, especially in overdose	
General disorders	Fevera, malaiseb		Fatiguea

[a] Usually attributable to Methocarbamol

[b] Usually attributable to Paracetamol

[c] Usually attributable to Methocarbamol and Paracetamol

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the national reporting system.

4.9 Overdose

Methocarbamol:

Little information is available on the acute toxicity of methocarbamol. The cases of methocarbamol overdose reported occurred with concomitant intake of alcohol and other CNS

depressants and included the following symptoms: nausea, dizziness, blurred vision, hypotension, seizures and coma. Particular cases of intake of more than 22-30 grams of methocarbamol without severe toxicity or of survival/recovery after 30-50 grams intake have been reported. In both cases, the main symptom was extreme drowsiness. Treatment was symptomatic and they recovered without other effects. However, cases of fatal overdose have been reported.

Treatment of overdose with methocarbamol includes symptomatic and supportive treatment. Supportive measures include keeping an open airway, monitoring urine excretion and vital signs and administration of intravenous fluids, if necessary. The efficacy of haemodialysis in this overdose is not known.

Paracetamol:

The symptoms of paracetamol overdose include dizziness, vomiting, loss of appetite, jaundice, abdominal pain and renal and hepatic impairment. After an overdose the patient should be taken quickly to a medical center, even if no significant symptoms or signs have appeared. Although the signs and symptoms may cause death, they s may not appear immediately after intake, but from the third day onwards. Death may occur due to hepatic necrosis. Acute renal failure can also occur.

Paracetamol overdose has four phases, starting after intake of the overdose:

- **PHASE I** (12-24 hours): nausea, vomiting, diaphoresis and anorexia
- **PHASE II** (24-48 hours): clinical improvement; AST, ALT, bilirubin and prothrombin levels rise
- **PHASE III** (72-96 hours): hepatotoxicity peak; AST values of 20,000 may occur.
- **PHASE IV** (7-8 days): recovery

Hepatotoxicity may occur. The minimum toxic dose in adults is 6g and over 100 mg/Kg of body weight in children. Doses higher than 20-25g are potentially fatal. Symptoms of hepatotoxicity include nausea, vomiting, anorexia, malaise, sweating, abdominal pain and diarrhea. Hepatotoxicity does not become apparent until 48-72 hours after intake. In the event of doses higher than 150 mg/kg or when it is not possible to establish the amount taken, a sample of *paracetamol* in serum should be taken 4 hours after the overdose. In case of hepatotoxicity, liver function tests should be carried out and repeated every 24 hours. Liver failure may lead to encephalopathy, coma and death.

Paracetamol plasma levels higher than 300 µg/ml 4 hours after the overdose have been associated with liver damage in 90% of patients. This begins to occur when plasma levels of *paracetamol* are less than 120 µg/ml 4 hours after the overdose, or less than 30 µg/ml 12 hours after the overdose.

Chronic intake of doses greater than 4g per day may give rise to transitory hepatotoxicity. The kidneys may suffer tubular necrosis and the myocardium may be damaged.

Treatment: aspiration and stomach pumping should be performed in all cases, preferably within 4 hours of the overdose intake.

There is a **specific antidote** for *paracetamol* toxicity: *N-acetylcysteine.* The recommended dose is 300 mg/kg (equivalent to 1.5 ml/kg 20% aqueous solution; pH 6.5) administered **intravenously** over a period of 20 hours and 15 minutes, according to the following scheme for adult patients:

- Attack dose: 150 mg/kg (equivalent to 0.75 ml/kg 20% aqueous solution; pH: 6.5), administered slowly intravenously, or diluted in 200 ml 5% dextrose, over 15 minutes.

- Maintenance dose:
  a) Initially, 50 mg/kg (equivalent to 0.25 ml/kg 20% aqueous solution ; pH: 6.5), in 500 ml 5% dextrose in slow infusion over 4 hours; followed by
  b) 100 mg/kg (equivalent to 0.50 ml/kg 20% aqueous solution; pH: 6.5}, in 1000 ml 5% dextrose in slow infusion over 16 hours.

The efficacy of the antidote is higher if administered within 8 hours of the overdose. Its effectiveness decreases progressively after the eighth hour, becoming ineffective after the 15th hour.

Administration of *N-acetylcysteine* 20% aqueous solution can be discontinued when plasma levels of paracetamol are below 200 µg/ml .

Adverse effects of *N-acetylcysteine* taken intravenously: skin rashes and anaphylaxis have been observed very rarely, generally between 15 minutes and 1 hour after starting the infusion.

When administered **orally,** *N-acetylcysteine* must be given within 10 hours from the overdose. The recommended dose for adults is:

- initial dose of 140 mg/kg of body weight
- 17 doses of 70 mg/kg of body weight, one every 4 hours

Prior to administration, each dose should be diluted to 5% with cola, grape or orange juice or water due to its unpleasant odour and to its irritating or sclerosing properties. If vomiting occurs within one hour after administration, repeat the dose. If necessary, the antidote (diluted in water) can be administered via duodenal intubation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: muscle relaxants; carbamic acid esters; methocarbamol, combinations excluding psycholeptics.

ATC Code: M03BA53

Methocarbamol:

Methocarbamol is a centrally acting muscle relaxant. It produces its muscle-relaxant effect by inhibiting polysynaptic reflexes in the spinal cord and subcortical centers. At therapeutic doses, methocarbamol does not interfere with the physiological tone or contractility of the skeletal muscles or the motility of the smooth muscles.

Paracetamol:

Paracetamol is an analgesic with antipyretic properties.

The exact mechanism of action of paracetamol is not known, although it is known that it acts on the Central Nervous System and, to a lesser extent, through a peripheral action by blocking generation of pain impulse. It seems that paracetamol increases the pain threshold by inhibiting prostaglandin synthesis, by means of blocking cyclooxygenase enzymes (specifically COX-3) in the Central Nervous System. However, it does not significantly inhibit cyclooxygenase in peripheral tissues.

Paracetamol stimulates the activity of the descending serotoninergic pathways which block the transmission of nociceptive signals from peripheral tissues to the spinal cord. In this regard,

some experimental data indicate that the intraspinal administration of different subtypes of serotonergic receptor antagonists can block the antinociceptive effect of paracetamol.

Its antipyretic action is related to the inhibition of PGE_1 synthesis in the hypothalamus, the organ which coordinates the thermoregulation process.

5.2 Pharmacokinetic properties

Methocarbamol:

Absorption
Methocarbamol is rapidly and completely absorbed after oral administration, with a time to maximum plasma concentration of around 1-3 hours. Its muscle relaxant effects become apparent 30 minutes after oral administration.

Distribution
Once methocarbamol enters systemic circulation, it is widely distributed throughout the body being the plasma protein binding in healthy volunteers 46-50%. In laboratory animals, the highest concentrations are detected in the liver and kidneys. This drug is able to cross the placental barrier, although it is not known whether it is excreted in breast milk.

Biotransformation
Methocarbamol is extensively metabolised in liver by dealkylation and hydroxylation.

Clearance

In healthy volunteers, plasma clearance of methocarbamol ranges from 0.2 to 0.8 l/h/kg, with an elimination half-life of 1-2 hours. Methocarbamol is eliminated mainly in urine as glucuronide and sulphate conjugates of its metabolites. A small proportion is also excreted in feces.

Older patients

In older patients, the elimination half-life of methocarbamol increases slightly compared to younger patients. Moreover, plasma protein binding slightly decreases (41-43% *vs.* 46-50%).

Patients with hepatic impairment

In 8 patients with liver failure due to alcohol cirrhosis, methocarbamol total clearance was reduced approximately 70% compared to that of healthy subjects (11.9 L/h) and the elimination half-life increased up to 3.38 h (± 1.62) compared to 1.11 h (± 0.27) in healthy subjects. The fraction of methocarbamol bound to plasma proteins was decreased to 40-50% compared to that in age and weight-matched healthy subjects (46-50%).

Patients with renal impairment

In patients with renal insufficiency, methocarbamol clearance is also reduced.

Methocarbamol clearance in 8 renally impaired patients on maintenance hemodialysis was reduced about 40% compared to healthy subjects, although the elimination half-life was similar in both groups (1.2 *vs.* 1.1, respectively).

Paracetamol

5.2.1 Absorption
The bioavailability of paracetamol after oral administration is 75-85%. It is absorbed extensively and rapidly; maximum plasma levels are achieved within 0.5-2 hours, depending on the pharmaceutical form. Drugs which delay gastric emptying also delay paracetamol absorption.

5.2.2 Distribution
Once absorbed, paracetamol is distributed uniformly throughout the body, with its lowest levels in the adipose tissue and the cerebrospinal fluid. Plasma protein binding is 10%. The time until its maximum effect is 1-3 hours and the effect lasts for 3-4 hours.

5.2.3 Biotransformation
Paracetamol undergoes first-pass metabolism in the liver, showing linear kinetic behaviour. However, this linearity disappears when doses higher than 2g are administered. *Paracetamol* is primarily metabolised in the liver (90-95%) and more than 90% is metabolised by conjugation of its hydroxyl group with glucuronic acid and sulphate groups. However, 5% of the administered dose of paracetamol is oxidized by the cytochrome P450, resulting in formation of N-acetyl-p-benzoquinoneimine (NAPQI) which is responsible for the hepatotoxicity. The small amount of NAPQI formed with therapeutic doses of paracetamol is readily rendered nontoxic by conjugation to the reduced glutathione (sulphhidryl group donor). When glutathione reserves are depleted to less that 70% or more, NAPQI cannot be detoxified, resulting in centrilobular necrosis. At high doses, paracetamol can saturate the primary mechanisms of liver metabolism and these alternative metabolic pathways are used, yielding hepatotoxic and possibly nephrotoxic metabolites, due to glutathione depletion.

5.2.4 Clearance:
Paracetamol is mainly eliminated in urine as a conjugate with glucoronic acid and, to a lesser extent, with sulphate groups; less than 5% is excreted unaltered. Its elimination half-life is 1.5-3 hours, increasing in cases of overdose, in patients with liver insufficiency, older patients and children.

5.3. Preclinical safety data

Paracetamol:

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

Therapeutic doses of paracetamol have no toxic effects and only very high doses can cause centrilobular hepatic necrosis in animals and humans. Very high doses can also cause methemoglobinemia and oxidative hemolysis in dogs and cats, but rarely in humans.

In studies investigating the acute, subchronic and chronic toxicity of paracetamol in the rat and mouse, gastrointestinal lesions, blood count changes, degeneration of the hepatic and renal parenchyma and even necrosis were observed. These changes are, on the one hand, attributed to the mechanism of action and, on the other, to the metabolism of paracetamol. The metabolites are probably responsible for the toxic effects and the corresponding organic changes in humans. Moreover, during long term use (i.e. 1 year) very rare cases of reversible chronic aggressive hepatitis have been described in the range of therapeutic doses. At subtoxic doses, symptoms of intoxication can occur following a 3-week intake period. Paracetamol should therefore not be administered over a long period of time or at high doses.

Extensive investigations showed no evidence of any relevant genotoxic risk of paracetamol in the therapeutic, i.e. non-toxic, dose range.

Long-term studies in rats and mice yielded no evidence on relevan carcinogenic effects at non-hepatotoxic dosages of paracetamol.

Fertility

Chronic toxicity studies in animals show that, at high doses, *paracetamol* may cause testicular atrophy and inhibit spermatogenesis; the importance of this fact with regard to its use in humans is unknown.

Paracetamol in hepatotoxic doses showed genotoxic and carcinogenic potential (liver and bladder tumours), in rat and mice. However, it is considered that this genotoxic and carcinogenic activity is related with changes in the metabolism of paracetamol when taking high doses and does not represent a risk for the clinical use.

Methocarbamol:

The acute toxicity of methocarbamol is comparatively low. In animal testing, the following signs of intoxication were observed: ataxia, catalepsy, cramps and coma. No chronic toxicity studies have been carried out. Reproductive toxicity of methocarbamol has not been evaluated. There are no long-term animal studies to assess the effect of methocarbamol on mutagenesis. Long.term studies to evaluate the carcinogenic potential of methocarbamol have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stearic acid
Maize starch pregelatinised
Croscarmellose sodium
Magnesium stearate
Silica, colloidal anhydrous
Povidone
Glycerol distearate
Sodium starch glycolate (derived from potato)
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 30ºC.

6.5 Nature and contents of container

50 tablets in a PVC-aluminium blister pack.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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