1.5 Product Information

1.5.1 Summary of Product Characteristics (SPC)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLEXDOL® tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains :

Ibuprofen	200 mg
Methocarbamol	500 mg

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

3. PHARMACEUTICAL FORM

Tablet
Box of 10 tablets in PVC/aluminium blister pack.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicine reduces the pain associated with muscles contractions, such as backache, tensions in the muscles of the neck, pulled muscles and sprains.

4.2 Posology and method of administration

Posology
The medicine is only for adults (aged over 15 years)
Take the tablets with a glass of water, preferably at the start of meals.
1 or 2 tablets every 4 to 6 hours. Do not exceed 6 tablets per 24 hours, unless otherwise prescribed by the doctor.

Method of administration
Oral use.

4.3 Contraindications

- History of allergy to methocarbamol,
- History of allergy or asthma triggered by taking ibuprofen or a related medicine, particularly other non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid,
- History of allergy to other constituents of the tablet,

- Active stomach or duodenal ulcer
- Serious liver disease,
- Serious kidney disease,
- Serious heart disease,
- Systemic lupus erythematosus,
- Myasthenia (serious muscle disease),
- History of convulsive attacks,
- After 5 complete months of pregnancy (24 weeks of amenorrhea).

4.4 Special warnings and precautions for use

Concomitant consumption of alcoholic beverage should be avoided.
This medicine should be used *WITH CARE* in case of renal insufficiency: the physician may decide to change the dose.
At high doses, above 1200 mg/day, ibuprofen has anti-inflammatory properties and can occasionally cause serious risks as observed with anti-inflammatory drugs.
BEFORE TAKING THIS MEDICINE, THE PHYSICIAN SHOULD BE INFORMED IN CASE OF:
• history of asthma associated with chronic rhinitis, chronic sinusitis or nasal polyps. The administration of ibuprofen can lead to an asthma attack, particularly in some subjects allergic to acetylsalicylic acid or NSAIDs.
• concomitant anticoagulant treatment. This medicine can lead to serious gastro-intestinal events.
• history of digestive disorders (hiatus hernia, haemorrhage of the digestive tract, history of stomach or duodenum ulcer).
• heart, liver or kidney disease.
• chickenpox.
This drug is not recommended in case of serious skin infections.

DURING THE TREATMENT, IN CASE OF:
• vision disorder, INFORM THE PHYSICIAN,
• gastro-intestinal haemorrhage (blood in the mouth, presence of blood in the faeces or black coloration of the faeces), DISCONTINUE THE TREATMENT AND CONTACT A PHYSICIAN OR AN EMERGENCY MEDICAL SERVICE IMMEDIATELY.
• burn like signs on skin or mucous membranes (redness with blisters, ulceration), DISCONTINUE THE TREATMENT AND CONTACT A PHYSICIAN OR AN EMERGENCY MEDICAL SERVICE IMMEDIATELY.
• signs suggesting allergy to this medicine, particularly an asthma attack or sudden swelling of the face and neck, DISCONTINUE THE TREATMENT AND CONTACT A PHYSICIAN OR AN EMERGENCY MEDICAL SERVICE IMMEDIATELY.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction related to ibuprofen

Hyperkalaemia risk related:

Some drugs or therapeutic classes can be the cause of hyperkalaemia: potassium salts, diuretics, angiotensin II-antagonists, ACE inhibitors, NSAIDs, heparin (low molecular weight heparin), cyclosporine, tacrolimus and trimethoprim.
Hyperkalaemia occurrence can depend on co-associated factors. The risk is increased in case of concomitant use of the drugs listed above.

Platelet anti-aggregating risk related
Due to their platelet anti-aggregating properties, many drugs are involved in this type of interaction: acetylsalicylic acid and NSAIDs, ticlopidine and clopidogrel, tirofiban, eptifibatid and abciximab, iloprost.
Concomitant use of different platelet anti-aggregating drugs, or concomitant use with heparin and heparin analogues, oral anti-coagulants and thrombolytic increases the risk of bleeding, this should be taken into account by maintaining a clinical and biological monitoring.

Concomitant administration of ibuprofen with the following product required rigorous patient monitoring:

The following combinations are not recommended:
Others NSAIDs (acetylsacylic acid and salicylates): increase of gastrointestinal ulceration or bleeding risk.

Oral anticoagulants: increase of bleeding risk by the anti-coagulant (platelet function inhibition and gastrointestinal mucosa membrane aggression by NSAIDs).
If concomitant use cannot be avoided, clinical and biological monitoring is required.

Heparins (at curative doses) or used in elderly patients: increase of bleeding risk (platelet function inhibition and gastrointestinal mucosa membrane aggression by NSAIDs).
If concomitant use cannot be avoided, clinical and biological monitoring is required. NSAIDs treatment should not exceed a few days.

Lithium: increase in serum lithium level (ibuprofen reduces renal clearance of lithium).
If concomitant use cannot be avoided, serum lithium levels should be frequently performed and lithium dose should be adapted during the concomitant use and at the end of NSAID treatment.

Methotrexate used at more than 15 mg weekly: increase of haematological methotrexate toxicity (anti-inflammatory drugs reduces the renal clearance of methotrexate).

Antacids: a bioavailability study has shown that there was no interference with the absorption of ibuprofen when given in conjunction with an antacid containing aluminium hydroxide and magnesium hydroxide.
Caution should be exercised during the following combinations:
Diuretics, ACE inhibitors and angiotensin II-antagonists: risk of acute renal insufficiency, in patients with impaired renal function (elderly patient and/or dehydrated patient), due to glomerular filtration reduction (inhibition of vasodilator prostaglandins by NSAIDs).
Moreover, the antihypertensive effect is reduced.
The patient should be hydrated. Renal function should be monitored when the treatment is initiated.

Antihypertensive: ibuprofen can interfere with blood pressure control in certain patients under treatment for mild to moderate hypertension.

Methotrexate used at less than 15 mg weekly: increase of haematological methotrexate toxicity (anti-inflammatory drugs reduces the renal clearance of methotrexate). Weekly control of haemogram is recommended during the first weeks of concomitant treatment. A thorough monitoring is required in case of renal function alteration (even slight) and in elderly patient.

Following combinations should be taken into account:
Others platelets anti-aggregating drugs (abciximab, eptifibatide, clopidogrel, iloprost, ticlopidine and tirofiban), heparins used at preventive doses: increase of bleeding risk.

Others hyperkaliaemic drugs (potassium salts, diuretics, angiotensin II-antagonists, ACE inhibitors, NSAIDs, heparin (low molecular weight heparin), cyclosporine, tacrolimus and trimethoprim. Risk of hyperkalaemia

Beta-blockers: (extrapolation of effects studied with indomethacin) reduction of antihypertensive effect (inhibition of vasodilator prostaglandins by NSAIDs)
Cyclosporine, tacrolimus: risk of additive nephrotoxic effects in elderly patients.
Coumarin-type: numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding. The doctor should be cautious when administering ibuprofen to patients on anticoagulants.
Digoxin: ibuprofen has been shown to increase serum digoxin concentration. Increase monitoring and dosage adjustments of digitalis glycoside may be necessary during concurrent ibuprofen therapy and following discontinuation of ibuprofen therapy;
H_2 antagonists: in studies with human volunteers, coadministration with cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.
Hypoglycaemic agents: ibuprofen may increase hypoglycaemic effects or oral antidiabetic agents and insulin.

Interaction related to methocarbamol
Following combinations are not recommended:
Alcohol: alcohol may increase drug sedative effect. Driving vehicles and using machines may then be dangerous due to reduced vigilance.
Avoid taking alcoholic beverages and drugs containing alcohol.

Following combinations should be taken into account:
Others CNS depressants: some anti-depressant drugs, sedative anti-histaminic, barbiturates, benzodiazepines, clonidine and related drugs, hypnotics, morphine derivatives (analgesic & antitussive) and neuroleptics, may increase CNS depression. Driving vehicles and using machines may then be dangerous due to reduced vigilance.

4.6 Pregnancy and lactation

The use of this medicine is not recommended during pregnancy and breastfeeding.

4.7 Effects on ability to drive and use machines

The patients who drive vehicles and use machines should be made aware of the risk of drowsiness and dizziness.

4.8 Undesirable effects

Effects associated with methocarbamol:
Risk of drowsiness, rarely skin reactions, fever, nausea, dizziness, headaches, loss of appetite, superficial inflammation of the eye, vision disorders.
Methocarbamol can cause a brown or green coloration of the urine, which is not harmful.

Effects associated with ibuprofen:
• Allergic reactions may occur:
- skin: eruption, itching, oedema, urticaria, aggravation of chronic urticaria,
- respiratory system: asthma attack,
- generalised: sudden swelling of the face and neck (Quincke's oedema).

• In some rare cases, gastro-intestinal haemorrhage may occur. These are more frequent at higher doses.
• Exceptionally, headaches accompanied by nausea, vomiting and stiffness of the neck have been observed.
• Exceptionally, serious skin infections have been observed during chickenpox.
• Very exceptionally blistering symptoms of the skin or mucous membranes can occur (burning sensation accompanied by redness with blisters, formation of ulcers).
In all these cases, the treatment must be immediately discontinued.
• During the treatment, it is possible that the following may occur:
- digestive tract disorders: stomach ache, vomiting, nausea, diarrhoea, constipation,
- exceptionally: vertigo or headache, rare vision disorders, significant reduction in the urines output, renal insufficiency, changes in hepatic enzymes levels or blood formula alteration (reduction in the white or red cells) potentially serious.

In all these cases, the physician must be informed.

4.9 Overdose

An overdose of methocarbamol may cause excessive drowsiness, blurred vision, hypotension, convulsions and coma. In case of methocarbamol overdose, vital signs should be monitored and specific correctives treatments applied.

Observed symptoms in case of ibuprofen overdose:
- Gastrointestinal: stomach-ache, diarrhoea, nausea vomiting, and epigastric pain.
- CNS: agitation, headache, vertigo, drowsiness, nystagmus ataxia, miosis, tinnitus, convulsion, coma in severe cases
- Renal: renal perfusion and glomerular filtrate decrease
- Metabolic: acidosis, hypothrombinaemia, hyperkalaemia
- Hepatic disorders
- Respiratory: apnoea

Treatment:
Gastric lavage.

If the gastric lavage is not sufficient, hospitalisation should be considered.
Ibuprofen antidote: not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Methocarbamol
Pharmacotherapeutic class: Muscle relaxant
Methocarbamol is effective in reducing muscle spam and pain in acute musculoskeletal disorders secondary to trauma and inflammation.
The precise mechanism of action of methocarbamol is not known. Methocarbamol is thought to act on the central nervous system, perhaps depressing polysynaptic reflexes.

Ibuprofen
Pharmacotherapeutic class: other analgesics and antipyretics.
ATC Code: N02B
Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID). Ibuprofen is a propionic acid derivative.
It has the following properties:
- Antalgic
- Antipyretic
- Anti-inflammatory
- Short term platelet function inhibition

All these properties are due to inhibition of prostaglandins synthesis.

5.2 Pharmacokinetic properties

At therapeutic doses, ibuprofen pharmacokinetic is linear.
Absorption
Maximal plasma concentration is obtained in approximately 90 minutes after ibuprofen oral administration.
After a single dose, the maximal serum concentration is proportional to the dose (C_{max} 17 ± 3, 5 µg/ml for 200 mg tablet and 30, 3 ± 4, 7 µg/ml for 400 mg tablet). Ibuprofen absorption is delayed by food.
When methocarbamol is administrated by oral route, it is absorbed from the gastrointestinal tract. Animal studies indicate that absorption occurs in small intestine. In comparative bioavailability study, following oral administration peak plasma concentration was reached in approximately 45 minutes, when methocarbamol was administered in combination with ibuprofen. The plasma half-life of methocarbamol administered alone was 1.25±0.27 hours and 1.30 ± 0.29 hours when administrated in combination

Distribution
Ibuprofen administration does not lead to accumulation phenomenon. About 99 % of ibuprofen is bound to plasmatic proteins.

Ibuprofen is retrieved in the synovial liquid, at stable concentrations, 2 to 8 hours after administration; maximal synovial concentration is approximately equal to third part of maximal plasma concentration.
Ibuprofen excretion in breast milk after intake of 400 mg dose every 6 hours was below 1 mg per 24 hours.

Metabolism
Ibuprofen does not show enzymatic inducing effects. 90% of ibuprofen is metabolized in inactive metabolites.
Methocarbamol has been shown to be metabolized in humans by dealkylation, hydroxylation and conjugation with glucuronic acid and sulphate, presumably in the liver. The metabolites are identified:
- 3-(2-hydroxyphenoxy), propane-1,2-diol-1-carbamate
- 3-(4-hydroxy-2-methoxyphenoxy)-propane-1,2-diol-1-carbamate.

The precise mechanism of action of methocarbamol is not known. Methocarbamol is thought to act on the central nervous system, perhaps depressing polysynaptic reflexes.

Excretion
Ibuprofen is mainly eliminated in urine. Excretion is complete within 24 hours :10% in unchanged form and 90% as metabolites, mainly glucurono-conjugates. The excretion half-life is approximately 2 hours.
Studies in humans dosed with radio-labelled (C^{14}) indicated that 97 to 99% of the administrated radioactivity is recovered in the urine over 3 days.
Extremely small amounts of unchanged methocarbamol have been recovered in faeces.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose, sodium starch glycolate, maize starch, povidone K-30, talc, magnesium stearate.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store in the original package, protect from heat, light and moisture
Store below 30 °C.

6.5 Nature and contents of container
Box of 10 tablets packed in PVC-ALU blister.

6.6 Special precautions for disposal and other handling
No special requirements.

7. DISPENSATION
☐ Over-the counter medicine ☒ Prescription only medicine

List II

8. MARKETING AUTHORISATION HOLDER
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