Package leaflet: Information for the user

Combileve 500 mg/200 mg film-coated tablets

Paracetamol and Ibuprofen

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- You should not take the product for longer than 3 days
- You must talk to a doctor if you do not feel better or if you feel worse after 3 days.

What is in this leaflet

1. What Combileve 500 mg/200 mg film-coated tablets are and what are they used for

Combileve 500 mg/200 mg film-coated tablets contains two active substances (which make the medicine work). These are **ibuprofen** and **paracetamol.**

Ibuprofen belongs to a group of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs). Paracetamol works in a different way to ibuprofen, but both active substances work together to reduce pain.

Combileve 500 mg/200 mg film-coated tablets is used for the short-term symptomatic treatment of mild to moderate pain.
This medicine is especially suitable for pain that cannot be relieved by paracetamol or ibuprofen alone.
Combileve 500 mg/200 mg film-coated tablets is used in adults aged 18 years and over.

You must talk to a doctor if you do not feel better or if you feel worse after 3 days.

2. What you need to know before you take Combileve 500 mg/200 mg film-coated tablets

Do not take Combileve 500 mg/200 mg film-coated tablets if you:
- are already taking **any other paracetamol containing medicine.**

- are **allergic to ibuprofen**, **paracetamol** or any of the other ingredients of this medicine (listed in section 6).
- have a history of allergic reactions (e.g. bronchospasm, angioedema, asthma, rhinitis or urticaria) **associated with acetylsalicylic acid or other NSAIDs.**
- have an **active or recurrent peptic ulcer** (i.e. stomach or duodenal ulcer) **or bleeding** (two or more distinct episodes of proven ulceration or bleeding).
- have a **history of gastrointestinal bleeding or perforation related to previous NSAIDs therapy**.
- have **cerebrovascular or other active bleeding**.
- have unexplained **blood formation disturbances.**
- suffer from **severe heart, liver or kidney failure.**
- are **severely dehydrated**, caused by e.g. vomiting, diarrhoea or insufficient fluid intake.
- are **in the last 3 months of pregnancy.**
- are **under 18 years old**.

Warnings and precautions
Talk to your doctor or pharmacist before taking Combileve 500 mg/200 mg film-coated tablets if you:
- have an **infection** - please see heading "Infections" below
- are **elderly**
- have **asthma** or have suffered from asthma
- have a **kidney, heart, liver or bowel disorder, hepatitis or difficulty urinating**
- are **concomitantly treated with medicines affecting liver function**
- have a **tendency to bleed**
- have **Gilbert's syndrome** (a rare hereditary metabolic disease with possible signs such as yellowing of the skin or whites of the eyes)
- have **systemic lupus erythematosus** (SLE) – a condition of the immune system affecting connective tissue resulting in joint pain, skin changes and disorder of other organs **or mixed connective tissue disease**
- have **gastrointestinal disorders or chronic inflammatory bowel disease** (e.g. ulcerative colitis, Crohn's disease)
- have an inherited **deficiency of** a certain enzyme called **Glucose-6-phosphate dehydrogenase**
- have inherited genetic or acquired disorder of certain enzymes that manifest with either neurological complications or skin problems or occasionally both i.e. **porphyria**
- have **haemolytic anaemia**
- have **hay fever, nasal polyps or chronic obstructive respiratory disorders** since there may be an increased risk of allergic reactions
- suffer from **chronic alcoholism**
- are **underweight or have chronic malnutrition**
- have a lack of total body water (**dehydration**)
- have recently **had a major surgery**
- are in the **first 6 months of pregnancy** or are **breastfeeding**
- are **planning to become pregnant**.

Side effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms.

The concomitant use with NSAIDs, including cyclo-oxygenase-2 specific inhibitors, increases the risk of adverse reactions and should be avoided.

During treatment with Combileve 500 mg/200 mg film-coated tablets, tell your doctor straight away if:

If you have severe illnesses, including severe renal impairment or sepsis (when bacteria and their toxins circulate in the blood leading to organ damage), or you suffer from malnutrition, chronic alcoholism or if you are also taking flucloxacillin (an antibiotic). A serious condition called metabolic acidosis (a blood and fluid abnormality) has been reported in patients in these situations when paracetamol is used at regular doses for a prolonged period or when paracetamol is taken together with flucloxacillin. Symptoms of metabolic acidosis may include: serious breathing difficulties with deep rapid breathing, drowsiness, feeling sick (nausea) and being sick (vomiting).

Warning: Taking higher doses than the recommended doses do not give better pain-relief, but cause the risk of serious liver damage. The maximum daily dose of paracetamol must therefore not be exceeded. Do not take other medicines also containing paracetamol (see also section "Do not take Combileve 500 mg/200 mg film-coated tablets" above). The symptoms of liver damage normally occur first after a couple of days. It is therefore important to seek medical advice immediately if you have taken more than recommended. See also section 3 "If you take more Combileve 500 mg/200 mg film-coated tablets than you should".

Anti-inflammatory/pain-killer medicines like ibuprofen may be associated with a small increased risk of heart attack or stroke, particularly when used at high doses. Do not exceed the recommended dose or duration of treatment.

You should discuss your treatment with your doctor or pharmacist before taking Combileve 500 mg/200 mg film-coated tablets if you:
- have heart problems including heart failure, angina (chest pain), or if you have had a heart attack, bypass surgery, peripheral artery disease (poor blood circulation in the legs due to narrow or blocked arteries), or any kind of stroke (including'mini-stroke' or transient ischaemic attack "TIA").
- have high blood pressure, diabetes, high cholesterol, have a family history of heart disease or stroke, or if you are a smoker.

Signs of an allergic reaction to this medicine, including breathing problems, swelling of the face and neck region (angioedema), chest pain have been reported with ibuprofen. Immediately stop taking Combileve 500 mg/200 mg film-coated tablets and contact your doctor or medical emergencies without delay if you notice any of these signs.

Skin reactions
Serious skin reactions including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) have been reported in association with ibuprofen treatment. Stop taking Combileve 500 mg/200 mg film-coated tablets and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

Infections
Combileve 500 mg/200 mg film-coated tablets may hide signs of infections such as fever and pain. It is therefore possible that Combileve 500 mg/200 mg film-coated tablets may delay appropriate treatment of infection, which may lead to an increased risk of complications. This has been observed in pneumonia caused by bacteria and bacterial skin infections related to chickenpox. If you take this medicine while you have an infection and your symptoms of the infection persist or worsen, consult a doctor without delay.

Gastrointestinal symptoms

Serious gastrointestinal side effects (affecting the stomach and intestines) have been reported with the use of NSAIDs, including ibuprofen. These can occur with or without warning symptoms. The risk of these side effects is higher in patients with a history of stomach or intestine ulcer, particularly if bleeding or perforation was also involved. Elderly patients are at greater risk of gastrointestinal side effects. You should discuss any history of gastrointestinal problems with your doctor, and remain alert for any unusual abdominal symptoms, including nausea, vomiting, diarrhoea, constipation, indigestion, abdominal pain, tar-like stools, or vomiting blood.

Prolonged use of painkillers
The prolonged use of analgesics for headaches can result in worsening them. If this situation is experienced or suspected, you should tell your doctor and discontinue the treatment.
The regular use of painkillers, particularly in combination with several pain-relieving medicines, may lead to permanent kidney damage with the risk of renal failure, a condition called analgesic nephropathy. This risk may be increased under physical strain associated with loss of salt and dehydration. Therefore, it should be avoided.

In prolonged use of ibuprofen, regular checking of the liver values, the kidney function as well as the blood count is required.

Children and adolescents
This medicine is contraindicated in children and adolescents under 18 years.

Other medicines and Combileve 500 mg/200 mg film-coated tablets
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
Do not use Combileve 500 mg/200 mg film-coated tablets with:
• other **paracetamol containing** products.

Combileve 500 mg/200 mg film-coated tablets may affect or be affected by some other medicines. For example:
- **corticosteroid** tablets
- **antibiotics** (e.g. chloramphenicol or quinolones)
- **flucloxacillin** (antibiotic) due to a serious risk of blood and fluid abnormality (called metabolic acidosis) that must have urgent treatment (see section 2).
- **anti sickness** medicines (e.g. metoclopramide, domperidone)
- **acetylsalicylic acid, salicylates or other NSAIDs** (including COX-2 inhibitors such as celecoxib or etoricoxib)
- medicines that are **anti-coagulants** (i.e. thin blood/prevent clotting e.g. acetylsalicylic acid, warfarin, ticlopidine)
- **cardiac glycosides** (e.g. digoxin), medicines to strengthen the heart
- medicines for **high cholesterol** (e.g. cholestyramine)
- **diuretics** (facilitating the excretion of excess water)
- medicines that **reduce high blood pressure** (ACE-inhibitors such as captopril, beta-blockers such as atenolol medicines, angiotensin-II receptor antagonists such as losartan)
- medicines to **suppress the immune response** (e.g. methotrexate, ciclosporine, tacrolimus)
- medicines for **mania or depression** (e.g. lithium or SSRIs- selective serotonin reuptake inhibitors)
- **mifepristone** (for pregnancy termination)
- **phenytoin**, a medicine to prevent seizures in epilepsy
- **zidovudine**, a medicine to treat HIV medicines (the virus that causes acquired immunodeficiency disease)

- medicines that **decrease gastric emptying**
- medicines to treat bacterial infections called **aminoglycosides**
- medicines to treat gout and gouty arthritis called **probenecid** and **sulfinpyrazone**
- antifungal medicines that **inhibit the liver enzyme CYP2C9** (e.g. voriconazole, fluconazole)
- other medicines that are known to **affect the liver** or that **induce liver microsomal enzymes** such as alcohol and antiepileptic medicines (e.g. carbamazepine, phenobarbital, lorazepam)
- medicines to treat diabetes (**sulfonylureas**)
- **ginkgo biloba** (an herbal medicine) can increase the risk of bleeding with NSAIDs
- medicines used **to treat tuberculosis** (e.g. **isoniazid**).

Some other medicines may also affect or be affected by the treatment of Combileve 500 mg/200 mg film-coated tablets.
You should therefore always seek the advice of your doctor or pharmacist before you use Combileve 500 mg/200 mg film-coated tablets with other medicines.

Combileve 500 mg/200 mg film-coated tablets with alcohol
Do not drink alcohol during treatment with this medicine. Alcohol may increase paracetamol toxicity in the liver.

Pregnancy, breast-feeding and fertility
Pregnancy
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
Do not take Combileve 500 mg/200 mg film-coated tablets if you are in the last 3 months of your pregnancy as it could harm your unborn child or cause problems at delivery. It can cause kidney and heart problems in your unborn baby. It may affect your and your baby's tendency to bleed and cause labour to be later or longer than expected. You should not take Combileve 500 mg/200 mg film-coated tablets during the first 6 months of pregnancy unless absolutely necessary and advised by your doctor. If you need treatment during this period or while you are trying to get pregnant, the lowest dose for the shortest time possible should be used.
If taken for more than a few days from 20 weeks of pregnancy onward, Combileve 500 mg/200 mg film-coated tablets can cause kidney problems in your unborn baby that may lead to low levels of amniotic fluid that surrounds the baby (oligohydramnios) or narrowing of a blood vessel (ductus arteriosus) in the heart of the baby. If you need treatment for longer than a few days, your doctor may recommend additional monitoring.

Breastfeeding
Only small amounts of paracetamol and ibuprofen and its metabolites pass into breast-milk. This medicine may be taken during breast-feeding if it is used at the recommended dose and for the shortest possible time.

Fertility
Combileve 500 mg/200 mg film-coated tablets may make it more difficult to become pregnant. Ibuprofen belongs to a group of medicines which may impair fertility in women. This is reversible after discontinuation of the medicine. You should inform your doctor if you are planning to become pregnant or if you have problems becoming pregnant.

Driving and using machines
Combileve 500 mg/200 mg film-coated tablets may cause dizziness, drowsiness, fatigue and visual disturbances in some people. This should be taken into consideration on occasions when high alertness is

required, e.g. driving. Be careful driving or operating machines until you know how Combileve 500 mg/200 mg film-coated tablets affects you.

Combileve 500 mg/200 mg film-coated tablets contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to take Combileve 500 mg/200 mg film-coated tablets

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

For oral use and for short term use only (not more than 3 days).
The lowest effective dose should be used for the shortest duration necessary to relieve symptoms.
If you have an infection, consult a doctor without delay if symptoms persist or worsen (see section 2).
Do not take Combileve 500 mg/200 mg film-coated tablets for more than 3 days. If your symptoms worsen or persist, consult your doctor.

Adults: Take 1 tablet **with** a glass of **water**, up to 3 times a day. Leave at least 6 hours between doses. If one tablet does not control symptoms, then a maximum of 2 tablets may be taken up to three times a day. **Do not take more than six tablets in any 24 hour period** (equivalent to 3000 mg Paracetamol, 1200 mg Ibuprofen a day).

To reduce the likelihood of side effects, take Combileve 500 mg/200 mg film-coated tablets with food.

Use in elderly
No special dose modifications are required. There is an increased risk of serious consequence of adverse reactions. The lowest possible dose should be used for the shortest possible duration.

Use in children and adolescents
Not for use by children and adolescents under 18 years.

Your dose may need to be reduced to a maximum of 4 tablets per day if you:
• have kidney problems
• have liver problems
• are weighing less than 50 kg
• suffer from chronic malnutrition
• are regularly drinking alcohol (chronic alcoholism)
• are not hydrated sufficiently

Contains paracetamol.
Do not take any other paracetamol-containing products.
Do not exceed the stated dose.
Immediate medical advice should be sought in the event of overdosage, because of the risk of irreversible liver damage.

If you take more Combileve 500 mg/200 mg film-coated tablets than you should

Talk to a doctor at once if you take too much of this medicine even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage. Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.
If you have taken more Combileve 500 mg/200 mg film-coated tablets than you should, or if children have taken this medicine by accident always contact a doctor or nearest hospital to get an opinion of the risk and advice on action to be taken.
The symptoms of overdose can include nausea, stomach pain, vomiting (may be blood streaked), gastrointestinal bleeding (see also part 4 below), headache, ringing in the ears, confusion and shaky eye movement (nystagmus), or more rarely diarrhoea. In addition, at high doses, vertigo, blurred vision, low blood pressure, excitation, disorientation, coma, hyperkalaemia (raised blood potassium level), increased prothrombin time/INR, acute renal failure, liver damage, respiratory depression, cyanosis and exacerbation of asthma in asthmatics, drowsiness, chest pain, palpitations, loss of consciousness, convulsions (mainly in children), weakness and dizziness, blood in urine, low levels of potassium in your blood, cold body feeling, and breathing problems have been reported.
The hazard of paracetamol overdose is greater in patients with non-cirrhotic alcoholic liver disease.
Symptoms may be limited to nausea, vomiting, anorexia, pallor, and abdominal pain and may not reflect the severity of overdose or the risk of organ damage.
The shorter the interval between intake and initiation of treatment with antidote (as few hours as possible), the greater the likelihood that hepatic injury can be prevented.

If you forget to take Combileve 500 mg/200 mg film-coated tablets
Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

With regard to the following side effects, it must be considered that they are largely dependent on the dose and vary from patient to patient.
The most commonly observed side effects are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence, constipation, indigestion, abdominal pain, tarry stool, vomiting of blood, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed. Particularly the risk of gastrointestinal bleeding occurring is dependent on the dose range and the duration of use.
Oedema, high blood pressure and heart failure have been reported in association with NSAID treatment.

STOP TAKING the medicine and tell your doctor if you experience:
Uncommon (may affect up to 1 in 100 people)
- signs of intestinal bleeding (severe stomach pain, vomiting blood or liquid with what looks like coffee granules, blood in the stools/motions, black tarry stools)

Very rare (may affect up to 1 in 10,000 people)
- symptoms of aseptic meningitis, inflammation of the brain lining such as: stiff neck, headache, feeling or being sick, fever or clouding of consciousness
- severe allergic reactions. Symptoms can include: swelling of the face, tongue or larynx, difficult breathing, fast heartbeats, low blood pressure (anaphylaxis, angioedema or severe shock)
- respiratory reactivity including asthma, worsening of asthma, wheezing, difficulty in breathing

- reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms [exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis].
- worsening of existing severe skin infections (you may notice a rash, blistering and discolouration of the skin, fever, drowsiness, diarrhoea and sickness), or worsening of other infections including chicken pox or shingles or severe infection with destruction (necrosis) of subcutaneous tissue and muscle, blistering and peeling of the skin

Not known (frequency cannot be estimated from the available data)
- a serious condition that can make blood more acidic (called metabolic acidosis), in patients with severe illness using paracetamol (see section 2)
- chest pain, which can be a sign of a potentially serious allergic reaction called Kounis syndrome.
- widespread rash, high body temperature and enlarged lymph nodes and an increase of eosinophils (a type of white blood cells) (DRESS syndrome).
- a red, scaly widespread rash with bumps under the skin and blisters, mainly localized on the skin folds, trunk, and upper extremities, accompanied by fever. The symptoms usually appear at the initiation of treatment (acute generalised exanthematous pustulosis).

Other possible side effects

Common (may affect up to 1 in 10 people):
- gastrointestinal complaints such as stomach pain, heartburn, indigestion, feeling sick, being sick, wind and constipation, diarrhoea, slight gastrointestinal blood loss that may cause anaemia in exceptional cases
- increase in sweating
- alanine aminotransferase increased, gamma-glutamyltransferase increased and liver function tests abnormal with paracetamol
- swelling and fluid retention, swelling of ankles or legs (oedema); fluid retention generally responds promptly to discontinuation of the combination
- increased levels of creatinine and urea in blood

Uncommon (may affect up to 1 in 100 people):
- central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness
- hives, itching
- rash various types
- gastrointestinal ulcers, potentially with bleeding and perforation or gastrointestinal bleeding, worsening of inflammation of the colon (colitis) and digestive tract (Crohn's disease), ulcerative stomatitis, gastritis
- decrease in haemoglobin, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, increase in platelets (blood clotting cells) number

Rare (may affect up to 1,000 people)
- abnormal dreams
- damage of the kidney tissue (papillary necrosis)
- high level of uric acid in your blood (hyperuricemia)
- abnormal sensation of the skin (tingling, pins and needles)

Very rare (may affect up to 1 in 10,000 people):

- blood formation disorders (agranulocytosis, anaemia, aplastix anaemia, haemolytic anaemia, leucopenia, neutropenia, pancytopenia and thrombocytopenia). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding, bruising and nose bleeds
- optic neuritis and somnolence, aseptic meningitis in patients with existing disorders (such as systemic lupus erythematosus and mixed connective tissue disease), symptoms include stiff neck, headache, nausea, vomiting, fever or clouding of consciousness
- visual disturbances; in this case, you must stop using Combileve 500 mg/200 mg film-coated tablets and see a doctor
- hearing loss, ringing in the ears, spinning sensation (vertigo), confusion, psychotic reactions, hallucinations, depression
- fatigue, generally feeling unwell
- exfoliative dermatoses
- red spotty rash on the skin (purpura)
- loss of hair
- high blood pressure, vasculitis
- inflammation of the oesophagus, inflammation of the pancreas, formation of intestinal diaphragm-like strictures
- liver dysfunction, liver damage (particularly in long term use), liver failure, acute hepatitis, yellowing of the skin and/or whites of the eyes, also called jaundice; in overdose paracetamol can cause acute liver failure, liver impairment, liver necrosis, and liver injury
- nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and acute and chronic renal failure
- fast or irregular heartbeats, also called palpitations, tachycardia, arrhythmia, and other cardiac dysrhythmias, heart failure (causing breathlessness, swelling), myocardial infarction

Frequency not known (cannot be estimated from available data)

- Skin becomes sensitive to light.

Medicines such as Combileve 500 mg/200 mg film-coated tablets may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. (See section 2).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Combileve 500 mg/200 mg film-coated tablets

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Combileve 500 mg/200 mg film-coated tablets contains

- The active substances are paracetamol and ibuprofen. Each film-coated tablet contains 500 mg paracetamol and 200 mg ibuprofen.
- The other ingredients are:
  Tablet core: maize starch, povidone K 30 (E1201), croscarmellose sodium (E468), cellulose microcrystalline (E460), silica colloidal anhydrous (E551), glycerol dibehenate (E471).
  Film-coating: opadry white (polyvinyl alcohol-partially hydrolysed, talc, titanium dioxide (E171), glyceryl monocaprylocaprate, sodium laurilsulfate).

What Combileve 500 mg/200 mg film-coated tablets looks like and contents of the pack

Combileve 500 mg/200 mg film-coated tablets are white to off white, oblong, biconvex film-coated tablets with dimensions of 21 mm x 10.5 mm (± 0.5 mm) and marked with double circle mark on one side.

The film-coated tablets are blister-packed in:
PVDC/PVC//Alu blisters of 10 film-coated tablets *or*
PVDC/PVC//Alu PET child-resistant blisters of 10 film-coated tablets.

Cardboard box with 1 blister (10 tablets) or 2 blisters (20 tablets) and package leaflet inside.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

Phoenix Labs
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Clonee
County Meath
Ireland

Manufacturer

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This leaflet was last revised in XXX 2025.