For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack.

Ibuprofen and Paracetamol Suspension

Combiflam® Suspension

COMPOSITION:

Each 5ml of Combiflam® Suspension contains Ibuprofen I.P. 100mg and Paracetamol I.P. 162.5mg in a flavoured syrup base.

Colour: Sunset Yellow FCF

INDICATIONS:

Management of mild to moderate pain and inflammation in conditions such as headache, including migraine, post-operative pain, dental pain, musculoskeletal and joint disorders, peri-articular disorders and soft tissue disorders (sprains and strains). It also reduces fever.

DOSAGE AND ADMINISTRATION

Children: If this product is required for more than 3 days in children aged 6 months and above, or if symptoms worsen, a doctor should be consulted.

Adults may use the Combiflam® tablets formulation.

SPECIAL POPULATIONS

Elderly patients

No special dosage adjustments are required. Due to possible undesirable effect profile *(Refer Special Warnings and Precautions for Use section)*, it is recommended to monitor the elderly particularly carefully.

Hepatic impairment

No dose adjustments are required in patients with mild to moderate impairment to hepatic function (patients with severe hepatic dysfunction *refer Contraindications section*).

Renal impairment

No dose adjustments is required in patients with mild to moderate impairment to renal function (patients with severe renal insufficiency refer *Contraindications section*).

CONTRAINDICATIONS

Combiflam® suspension is contraindicated in:

- Patients with known hypersensitivity to paracetamol, ibuprofen or any of the excipients.
- In patients with a history of hypersensitivity reactions (eg. bronchospasm, angioedema, asthma, rhinitis or urticaria) associated with acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- Patients with unclarified blood- formation disturbances.
- In patients with severe hepatocellular insufficiency
- Severe renal failure or severe hepatic failure *(Refer Special Warning and Precaution for Use Section)*.
- Severe heart failure (NYHA Class IV)

- Active, or history of recurrent or existing peptic ulcer/haemorrhages (two or more distinct episodes of proven ulceration or bleeding).
- Cerebrovascular or other active bleeding
- Patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake)
- Third trimester of pregnancy *(Refer Pregnancy, Lactation and Fertility Section).*

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction *(Refer Adverse reactions section)*

Severe cutaneous adverse reactions (SCARs):

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS), and Toxic epidermal necrolysis (TEN) have been reported with the use of Combiflam® suspension. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms or signs of SJS and TEN (e.g. progressive skin rash often with blisters or mucosal lesions) occur, patients should immediately stop Combiflam® suspension treatment and seek medical advice.

To avoid the risk of overdose:

Check that paracetamol is absent from the composition of other medicinal products taken concomitantly.

Caution is advised in patients with underlying sensitivity to aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs).

Combiflam® suspension should be used upon medical advice in patients with following pre-disposing factors:

- Glucose-6-phosphate-dehydrogenase deficiency
- Severe renal insufficiency and sepsis
- Mild to moderate hepatocellular insufficiency
- Gilbert´s syndrome
- Chronic alcohol use including recent cessation of alcohol intake
- Malnutrition and other sources of low glutathione reserves

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patient with severe illness pre-disposing factors (see above) who were treated with paracetamol at therapeutic dose for a prolonged period or combination of paracetamol and flucloxacillin. Symptoms of HAGMA may include serious breathing difficulties with deep rapid breathing, drowsiness, nausea and vomiting. Prompt discontinuation of paracetamol and close monitoring is recommended if symptoms of HAGMA appear. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see gastrointestinal and cardiovascular risks below)

Caution is required in patients with certain conditions, which may be made worse:

- Systemic lupus erythematosus and mixed connective tissue disease – increased risk of aseptic meningitis or hepatitis *(Refer Adverse reactions section)*
- Congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria)

- Gastrointestinal disorders (such as peptic ulcer, hiatus hernia or gastrointestinal bleeding) and chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease) *(Refer Adverse reactions section)*
- Hypertension and/or cardiac impairment as renal function may deteriorate *(Refer Contraindication and Adverse reactions section)*
- Renal impairment (*Refer Contraindication and Adverse reactions section)*
- Hepatic dysfunction (*Refer Contraindication and Adverse reactions section)*
- Directly after major surgery
- In patients who react allergically to other substances, as an increased risk of hypersensitivity reactions occurring also exists for them on use of Combiflam® suspension.
- In patients who suffer from hayfever, nasal polyps or chronic obstructive respiratory disorders as an increased risk exists for them of allergic reactions occurring. These may present as asthma attacks (so-called analgesic asthma), Quincke's edema or urticaria.

Gastrointestinal effects:

The use of Combiflam® suspension with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors, increases risk of adverse reactions *(Refer Interaction section)* and should be avoided.

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal *Refer Dosage and administration section)*

Cardiovascular and cerebrovascular effects:

Caution (discussion with physician or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating long term treatment for patients with risk factors for cardiovascular events (Eg. Hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Hypersensitivity reactions to Combiflam® suspension can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to Combiflam® suspension *(Refer Adverse reactions section)*.

Gastrointestinal bleeding, ulceration and perforation:

GI bleeding, ulceration and perforation which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

When GI bleeding or ulceration occurs in patients receiving ibuprofen containing products, the treatment should be withdrawn.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation *(Refer Contraindication section*) and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid, or other drugs likely to increase GI risk *(Refer Interaction section).*

Patients with a history of GI toxicity, particularly the elderly should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid *(Refer Interaction section).*

NSAIDs should be given with care to patients with a history of GI disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated *(Refer Adverse reactions section).*

Skin reactions:

Serious skin reactions, some of them fatal including bullous and exfoliative dermatitis, Steven-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs.

Patients appear to be at highest risk of these reactions early during therapy, the onset of the reaction occurring in most cases within the first month of treatment. The patient is advised to discontinue the intake of Combiflam® suspension at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with Combiflam® Suspension treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. Treatment should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of skin hypersensitivity.

Fixed Drug Eruption and Generalised Bullous Fixed Drug Eruption

Cases of Fixed Drug Eruption (FDE) and Generalised Bullous Fixed Drug Eruption (GBFDE) have been reported with ibuprofen.

Ibuprofen should not be reintroduced in patients with history of ibuprofen-related FDE or GBFDE.

Masking of symptoms of underlying infections:

Combiflam® Suspension can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia, serious cutaneous and soft tissue infections and bacterial complications to varicella. Use of Combiflam® Suspension should be avoided in case of varicella. When Combiflam® Suspension is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen *(Refer Section Adverse Reactions section).*

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs, including Combiflam® Suspension at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.

Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation.

In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit Combiflam® Suspension use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if Combiflam® Suspension treatment extends beyond 48 hours. Discontinue Combiflam® Suspension if oligohydramnios occurs and follow up according to clinical practice. *(Refer Pregnancy section)*.

Renal disorders

Renal tubular acidosis and hypokalemia may occur following ibuprofen overdose with/without a prolonged treatment period *(Refer Overdose section)*

Other notes:

Severe acute hypersensitivity reactions (e.g. anaphylactic shock) are observed very rarely. At the first signs of hypersensitivity reaction after taking/administering Combiflam® suspension therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

Ibuprofen, the active substance of Combiflam® suspension may temporarily inhibit the blood-platelet function (thrombocyte aggregation). Therefore, patients with platelet disorders should be monitored carefully.

In case of prolonged treatment with ibuprofen, liver and kidney parameters as well as blood picture need to be checked regularly.

Prolonged use of any type of analgesics for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

In general terms, the habitual intake of analgesics particularly on combination of several pain-relieving active substances, may lead to permanent renal damage with the risk of renal failure (analgesic nephropathy). This risk may be increased under physical strain associated with loss of salt and dehydration. Therefore, it should be avoided.

Through concomitant consumption of alcohol, active substance-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

Pediatric population

There is a risk of renal impairment in dehydrated children and adolescents.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes, such as certain antiepileptics (such as phenobarbital, phenytoin, carbamazepine, topiramate), rifampicin and alcohol. The induced

metabolism results in an elevated production of the hepatotoxic oxidative metabolite of paracetamol. Hepatotoxicity will occur if this metabolite exceeds the normal glutathione binding capacity.

Paracetamol may increase the risk of bleeding in patients taking warfarin and other antivitamin K. Patients taking paracetamol and antivitamin K should be monitored for appropriate coagulation and bleeding complications.

Co-administration of flucloxacillin with paracetamol may lead to high anion gap metabolic acidosis due to pyroglutamic acidosis, particularly in patients with risk factors.

This product (like any other paracetamol containing products) is contraindicated in combination with other paracetamol containing products – increased risk of serious adverse effects

The absorption rate of paracetamol may be increased by metoclopramide or domperidone.

Chelating resin can decrease the intestinal absorption of paracetamol and potentially decrease its efficacy if taken simultaneously. In general, there must be an interval of more than 2 hours between taking the resin and taking paracetamol, if possible.

Concomitant use of ibuprofen with	**Possible effects:**
Other NSAIDs, including salicylates:	The concomitant administration of several NSAIDs may increase the risk of gastrointestinal ulcers and bleeding due to a synergistic effect. The concomitant use of ibuprofen with other NSAIDs should therefore be avoided *(Refer Special Warning and precautions for use section).*
Digoxin:	The concomitant use of Combiflam® suspension with digoxin preparations may increase serum level of digoxin. A check of serum-digoxin is not as a rule required on correct use (maximum over 4 days).
Corticosteroids:	Corticosteriods as these may increase the risk of adverse reactions, especially of the gastrointestinal tract (gastrointestinal; ulceration or bleeding) *(Refer Special Warning and precautions for use section).*
Anti-platelet agents:	Increased risk of gastrointestinal bleeding *(Refer Special Warning and precautions for use section).*
Acetylsalicylic acid	Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects. Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is likely for occasional ibuprofen use
Anticoagulants:	NSAIDs may enhance the effect of anti-coagulants, such as warfarin *(Refer Special Warning and precautions for use section).*
Phenytoin:	The concomitant use of Combiflam® suspension with phenytoin preparations may increase serum level of phenytoin. A check of serum-phenytoin levels is not as a rule required on correct use (maximum over 4 days).

Selective serotonin reuptake inhibitors (SSRIs):	Increased risk of gastrointestinal bleeding *(Refer Special Warning and precautions for use section).*
Lithium:	The concomitant use of Combiflam® suspension with lithium preparations may increase serum level of lithium. A check of serum-lithium is not as a rule required on correct use (maximum over 4 days).
Probenecid and sulfinpyrazone:	Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.
Diuretics, ACE inhibitors, betareceptor-blockers and angiotensin-II antagonists	NSAIDs may reduce the effect of diuretics and other antihypertensive medicinal products. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor, betareceptor-blockers or angiotensin-II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.
Potassium sparing diuretics:	The concomitant administration of Combiflam® suspension and potassium-sparing diuretics may lead to hyperkalaemia.
Methotrexate:	The administration of Combiflam® suspension within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.
Ciclosporin:	The risk of a kidney-damaging effect due to ciclosporin is increased through the concomitant administration of certain nonsteroidal antiinflammatory drugs. This effect also cannot be ruled out for a combination of ciclosporin with ibuprofen.
Tacrolimus:	The risk of nephrotoxicity is increased if the two medicinal products are administered concomitantly
Zidovudine:	There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) hemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
Sulphonylureas:	Clinical investigations have shown interactions between nonsteroidal anti-inflammatory drugs and antidiabetics (sulphonylureas). Although interactions between ibuprofen and sulphonylureas have not been described to date, a check of blood-glucose values is recommended as a precaution on concomitant intake.
Quinolone antibiotics:	Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
CYP2C9 inhibitors:	Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors), an increased S(+)-ibuprofen exposure by approximately 80 to 100% has been shown. Reduction of the ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high dose (2400 mg/day) ibuprofen is administered with either voriconazole or fluconazole.

Mifepristone:	NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone

PREGNANCY LACTATION AND FERTILITY

PREGNANCY:

A large amount of data on pregnant women indicates neither malformative, nor feto/neonatal toxicity. Paracetamol can be used during pregnancy if clinically needed however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development.

During the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen 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 constriction/closure of the ductus arteriosus mostly resolving after treatment cessation and Pulmonary hypertension)
  - Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis

Use of NSAIDs, including Combiflam® Suspension, at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment (*Refer Special warnings and precautions for use).*

Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Combiflam® Suspension from gestational week 20 onward. Combiflam® Suspension should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

- 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 labor.

Consequently, Ibuprofen is contraindicated during the third trimester of pregnancy.

LACTATION:

Paracetamol is excreted in breast milk but not in a clinically significant amount. At therapeutic doses, it is possible to administer this medicinal product to breastfeeding mothers.

Ibuprofen and its metabolites can pass in low concentrations into the breast milk. No harmful effects to infants are known to date. Therefore, for short-term treatment with the recommended dose for pain and fever, interruption of breast-feeding would generally not be necessary**.**

FERTILITY

There is some evidence that drugs which inhibit cyclo-oxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

As central nervous undesirable effects such as tiredness and dizziness may occur on use of Combiflam® suspension at higher dosage, the ability to react and the ability to take part actively in road traffic and to operate machines may be impaired in isolated cases. This applies to a greater extent in combination with alcohol.

ADVERSE REACTIONS

Paracetamol

The following CIOMS frequency rating is used, when applicable:

Very common ≥ 10%; Common ≥ 1 and < 10%; Uncommon ≥ 0.1 and < 1%;

Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%; Not known (cannot be estimated from available data).

Blood and lymphatic system disorders

Very rare: thrombocytopenia, neutropenia, leucopenia

Not known: agranulocytosis, hemolytic anemia in particular in patients with underlying glucose 6-phosphate-deshydrogenase deficiency

Immune system disorders

Not known: Hypersensitivity such as anaphylactic shock, angioedema

Respiratory, thoracic and mediastinal disorders

Not known: bronchospasm *(Refer Special Warning and Precaution for Use Section).*

Skin and subcutaneous disorders:

Very rare: erythema, urticaria, rash

Not known: Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis, fixed drug eruption.

Hepatobiliary disorders

Not known: cytolytic hepatitis, which may lead to acute hepatic failure

Metabolism and nutrition system disorders

Not known: High anion gap metabolic acidosis due to pyroglutamic acidosis, in patients with pre-disposing factors.

Ibuprofen:

The following CIOMS frequency rating is used, when applicable:
Very common ≥ 10%; Common ≥ 1 and < 10%; Uncommon ≥ 0.1 and < 1%;
Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%; Not known (cannot be estimated from available data).

Infections and Infestations	Very rare	Combiflam® suspension can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection (including bacterial community-acquired pneumonia, serious cutaneous and soft tissue

		infections and bacterial complications to varicella) *(Refer Section Special Warning and Precaution for Use)*
		The symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or consciousness clouding have been observed under ibuprofen. Patients with autoimmune disorders (SLE, mixed connective-tissue disease) appear to be predisposed.
Blood and Lymphatic System Disorders	Very rare	Disturbances to blood formation (anemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis). The first signs may be fever, sore throat, superficial wounds in the mouth, influenza-like complaints, severe lassitude, nosebleeds and skin bleeding. The blood count should be checked regularly in long-term therapy.
Immune System Disorders	Uncommon	Hypersensitivity reactions with skin rashes and itching, as well as asthma attacks (possibly with drop in blood pressure).
	Very rare	Severe general hypersensitivity reactions. They may present as face oedema, swelling of the tongue, swelling of the internal larynx with constriction of the airways, respiratory distress, racing heart, drop in blood pressure up to life-threatening shock.
		If one of these symptoms occurs, which can happen even on first use, the immediate assistance of a physician is required.
Psychiatric Disorders	Very rare	Psychotic reactions, depression
Nervous System Disorders	Uncommon	Central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness
Eye Disorders	Uncommon	Visual disturbances
Ear and Labyrinth Disorders	Rare	Tinnitus
Cardiac Disorders	Very rare	Palpitations, heart failure, myocardial infarction
	Not known	Kounis syndrome
Vascular Disorders	Very rare	Arterial hypertension, vasculitis
Gastrointestinal Disorders	Common	Gastro-intestinal complaints such as pyrosis, abdominal pain, nausea, dyspepsia, vomiting, flatulence, diarrhea, constipation and slight gastro-intestinal blood losses that may cause anemia in exceptional cases
	Uncommon	Gastrointestinal ulcers, potentially with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis and Crohn's disease *(Refer Section Special Warning and Precaution for Use)*, gastritis
	Very rare	Esophagitis, pancreatitis, formation of intestinal diaphragm-like strictures.
		The patient is to be instructed to withdraw the medicinal product and to go to a physician immediately if severe pain in the upper abdomen or melaena or hematemesis occurs.
Hepatobiliary Disorders	Very rare	Hepatic dysfunction, hepatic damage, particularly in long-term therapy, hepatic failure, acute hepatitis

Skin and Subcutaneous Tissue Disorders	Uncommon	Skin rashes
	Very rare	Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome 17), alopecia. In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and infestations").
	Not known	photosensitivity reaction
Renal and Urinary Disorders	Rare	Kidney-tissue damage (papillary necrosis) and elevated uric acid concentrations in the blood may also occur rarely.
	Very rare	Formation of oedemas, particularly in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis that may be accompanied by acute renal insufficiency. Renal function should therefore be checked regularly.
Skin and subcutanueous tissue disorders	Not known	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Fixed drug eruption (FDE)* including Generalised Bullous Fixed Drug Eruption (GBFDE)*

(*) Although absorption of topically administered ibuprofen is low compared to oral administration, these skin systemic-mediated adverse events cannot be ruled out.

If appropriate, patients should be adequately informed that they should stop taking Combiflam® suspension immediately and consult a physician if they experience one of the following conditions:

- Severe gastro-intestinal complaints, pyrosis or abdominal pain
- Hematemesis
- Meleana or blood in the urine
- Cutaneous reactions, such as itching eruptions
- Respiratory distress and/or facial or laryngeal edema
- Fatigue combined with loss of appetite
- Sore throat, combined with aphthous ulcers, fatigue and fever
- Heavy epistaxis and cutaneous bleeding
- Abnormal fatigue combined with reduced urine excretion
- Edema of feet or legs
- Breast pain
- Visual disturbances

OVERDOSE

Paracetamol

Elderly persons, small children, patients with liver disorders, chronic alcohol consumption or chronic malnutrition, as well as patients concomitantly treated with enzyme-inducing drugs are at an increased risk of intoxication, including fatal outcome.

Signs and Symptoms:

Nausea, vomiting, anorexia, pallor, abdominal pain, generally appear during the first 24 hours of overdosage with paracetamol. Overdosage with paracetamol may cause hepatic cytolysis which can lead to hepatocellular insufficiency, gastrointestinal bleeding, metabolic acidosis, encephalopathy, disseminated intravascular coagulation, coma and death. Increased levels of hepatic transaminases, lactate deshydrogenase and bilirubin with a reduction in prothrombin level can appear 12 to 48 hours after acute overdosage. It can also lead to pancreatitis, acute renal failure and pancytopenia.

Management:

Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention.

Treatment involves gastric aspiration and lavage, preferably within 4 hours of ingestion.

Determinations of the plasma concentration of paracetamol are recommended.

Plasma concentration of paracetamol should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Where paracetamol intoxication is suspected, intravenous administration of SH group donators such as N-acetylcysteine within the first 10 hours after ingestion is indicated. Although N-acetylcysteine is most effective if initiated within this period, it can still offer some degree of protection if given as late as 48 hours after ingestion; in this case, it is taken for longer.

Further measures will depend on the severity, nature and course of clinical symptoms of paracetamol intoxication and should follow standard intensive care protocols.

Ibuprofen:

Signs and Symptoms:

The symptoms of overdose can include CNS-related symptoms such as headache, dizziness, light-headedness and unconsciousness (also myoclonic convulsions in children), abdominal pain, nausea, vomiting, gastrointestinal bleeding and hepatic and renal dysfunction, hypotension, respiratory depression and cyanosis.

Ibuprofen overdose may cause:

- metabolic acidosis

- Renal tubular acidosis and hypokalemia with/without prolonged treatment period. Symptoms may include reduced level of consciousness and generalized weakness (*Refer Warning/Precaution section*)

Management:

A specific antidote does not exist.

Oral administration of activated charcoal is to be considered, if the patient presents within 1 hour of ingestion of a potentially toxic amount.

INTERFERENCES WITH LABORATORY AND DIAGNOSTIC TEST

Effects on laboratory values

Intake of paracetamol may affect the laboratory determination of uric acid by phosphotungstic acid and of blood glucose by glucose oxidase-peroxidase.

Manufactured by:

Sanofi Consumer Healthcare India Limited

At: 182, Village - Gurumajra, Kishanpura, Tehsil - Baddi Dist. Solan (H.P.)- 174 101

Updated: April 2025

Source:

- CCDS V5for Paracetamol dated 23rd January 2025
- CCDS V10 for Ibuprofen dated 08th October 2024