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

**Paracetamol and Caffeine Tablets I.P.**
**Combiflam® Plus**

## COMPOSITION:

Each uncoated tablet contains
Paracetamol I.P. ……. 650 mg
Caffeine I.P. ……...50mg
Excipients ……q.s.

## INDICATIONS

For symptomatic relief from mild to moderate pain including, headache, migraine, toothache and musculoskeletal pain (body pain).

**Combiflam® Plus** contains paracetamol, which is an analgesic and antipyretic, and caffeine enhances the pain-relieving activity of paracetamol.

## DOSAGE AND ADMINISTRATION

Unless otherwise prescribed by the physician, the following dosages are recommended:

Adults and children over 12 years: 1 tablet, 3 to 4 times a day every 6 to 8 hours with a minimum gap of 4 hours in a 24 hour period. Do not exceed stated dose. If symptoms persist, seek medical advice.

**Combiflam® Plus** is not recommended in children under 12 years of age.

Do not take this medicine more than 3 days without medical advice

## CONTRAINDICATIONS

**Combiflam® Plus** is contraindicated in patients with hypersensitivity to paracetamol, caffeine or any of the excipients and in patients with severe hepatocellular insufficiency.

## SPECIAL WARNINGS AND PRECAUTIONS

**Related to Paracetamol component:**

Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction (See "Section Adverse Reactions").

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® Plus**. 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® Plus** 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® Plus** should be used upon medical advice in patients with:
- Mild-to-moderate hepatocellular insufficiency
- Chronic alcohol use including recent cessation of alcohol intake
- Low glutathione reserves
- Glucose-6-phosphate-dehydrogenase deficiency
- Gilbert´s syndrome

**Related to Caffeine component**

Caution is advised in patients with:
- Anxiety disorders (risk of enhancement)
- Arrhythmia (risk of tachycardia or extra systoles enhancement)

Excessive intake of caffeine (products with caffeine e.g. coffee, tea, foods, other drugs and beverages) should be avoided while taking this product (See Section Overdose).

**Related to Caffeine + Paracetamol component**

**Combiflam® Plus** should be used upon medical advice in patients with renal impairment

## INTERACTIONS

**Related to Paracetamol component:**
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 metabolic acidosis, particularly in patients presenting risk factors of glutathione depletion, such as sepsis, malnutrition or chronic alcoholism.

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.

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

**Related to Caffeine component:**

Caffeine may antagonise the sedative effect of other drugs (e.g. barbiturates, anti-histaminics).

Caffeine reduces excretion of theophylline.

The concomitant intake of gyrase inhibitors of the quinolone carbonic acid type (e.g., enoxacin, ciprofloxacin) can delay the elimination of caffeine and its degradation product paraxanthine.

CYP1A2 inhibitors (e.g., oral contraceptives, cimetidine, fluvoxamine, disulfiram, mexiletin) may reduce the caffeine metabolism in the liver.

## PREGNANCY AND LACTATION

### PREGNANCY
Because of the content of caffeine, **Combiflam® Plus** is not recommended during pregnancy.

The prolonged intake of high amounts of caffeine may lead to spontaneous abortion or premature birth in pregnant women.

Non-clinical studies have shown reproductive toxicity at very high doses.

### LACTATION

Paracetamol and caffeine are excreted in breast milk.
Caffeine ingested with breast milk may influence the condition and behaviour of the infant.
Lactation does not usually need to be discontinued if the product is taken for a short time only and in the recommended doses. Lactation should be discontinued in the case of prolonged use or intake of higher doses.

Use of this product during lactation is recommended under medical supervision.

## DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
None

## ADVERSE REACTIONS:

***Related to Paracetamol component***

**Blood and lymphatic system disorders**
Very rare: thrombocytopenia, neutropenia, leukopenia
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 (see section “Warnings and Precautions”)

**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: pyroglutamic acidosis, in patients with pre-disposing factors for glutathione depletion

***Related to Caffeine component***

**Psychiatric disorders**
Not know: anxiety, insomnia, restlessness and tremor

**Gastrointestinal disorders**
Not known: gastric disorders

**Cardiac disorders**
Not known: heart rate increased

## OVERDOSE

### Paracetamol:

***Related to Paracetamol component***

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

***Related to Paracetamol component***

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.

***Related to Caffeine component***

Symptoms of toxicity can occur at caffeine doses of 1 g and above (15 mg/kg if body weight is below 70 kg) if the dose is taken over a short period.

Early symptoms with acute caffeine poisoning are usually tremor and restlessness. These are followed by nausea, vomiting, tachycardia and confusion. With serious intoxication, delirium, seizures, tachycardia and arrhythmias, hypokalaemia and hyperglycaemia may occur.

***Related to the combination of Paracetamol and Caffeine***
Overdose of Paracetamol and caffeine can cause headache.

**MANAGEMENT**

***Related to Paracetamol component***

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.

***Related to the combination of Paracetamol and Caffeine***

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

**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.

**Storage:** Store protected from light and moisture at a temperature not exceeding 30 °C.
Keep out of reach of children.

**Presentation:**
Combiflam® Plus Tablets:
•Blister of 10 tablets
•20 Blisters in a carton

**Manufactured in India by:** Elysium Pharmaceuticals Ltd., At & Post: Dabhasa, Tal.: Padra, Dist.: Vadodara, Gujarat – 391 440.

**Marketed by:** Sanofi India Limited, Sanofi House, CT Survey No. 117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai - 400072

***Created: September 2021***

***Reference:***
*1. Ref: Paracetamol + caffeine CCDS v3 LRC dated 08th Jul2021.*
*2. Product Information Leaflet - Crocin Pain Relief (https://india-consumer.gsk.com/media/861691/crocin-pain-relief.pdf - as assessed on 03rd November 2020)*

*3. Final Guidance Document_ Acetaminophen Labelling Standard_Health Canada*