PROFESSIONAL INFORMATION FOR IBUGESIC FORTE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

IBUGESIC FORTE (200 mg / 250 mg / 10 mg capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each IBUGESIC FORTE capsule contains 200 mg ibuprofen, 250 mg paracetamol and 10 mg codeine phosphate.

Sugar free.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Capsules.

Size 0 capsule with red body and dark green cap containing a free flowing white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IBUGESIC FORTE is indicated for the relief of mild to moderate pain of inflammatory origin with or without fever.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE.

Adults: 1 to 2 capsules 6 hourly. Do not take more than 6 capsules in 24 hours.

If no effective pain relief is achieved, the patients should be advised to seek the views of a physician. IBUGESIC FORTE is for short term use and is not recommended for use beyond 4 days.

Paediatric population

Not recommended for children under twelve years of age.

4.3 Contraindications

IBUGESIC FORTE is contraindicated in:

- patients with known hypersensitivity to ibuprofen, paracetamol, codeine phosphate or to any of the excipients of IBUGESIC FORTE (see **section 6.1**)
- patients with acute respiratory depression
- concurrent use with Monoamine Oxidase Inhibitors (MAOIs) or within 14 days of stopping such treatment (see **section 4.5**)
- patients with diarrhoea associated with pseudomembranous colitis
- patients with severe liver impairment
- patients with peptic ulcer disease or gastrointestinal bleeding
- patients sensitive to aspirin or other nonsteroidal anti-inflammatory medicines
- patients with uncontrolled asthma or bronchospasm
- patients with nasal polyps associated with aspirin-induced bronchospasm
- patients with bleeding disorders
- avoid use of NSAIDs, including IBUGESIC FORTE in women around 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see **section 4.6**)
- heart failure

- patients with history of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including IBUGESIC FORTE
- patients with active or history of recurrent ulcer/haemorrhage/perforations.

4.4 Special warnings and precautions for use

IBUGESIC FORTE should be used with caution in the following:

- acute abdominal conditions - diagnosis or clinical course may be obscured
- acute asthma attack or respiratory impairment or disease – may decrease respiratory drive and increase airway resistance in these patients
- cardiac arrhythmias – may be induced or exacerbated
- convulsions or history thereof – may be induced or exacerbated
- alcoholism, drug abuse or dependence – patient is predisposed to drug abuse

  DEPENDENCE MAY DEVELOP WITH PROLONGED USE OF HIGH DOSES
- gallbladder disease or gallstones – may cause biliary tract spasm
- recent gastrointestinal tract surgery
- head injury, increased intracranial pressure or intracranial lesions – risk of respiratory depression and further increase in intracranial pressure. IBUGESIC FORTE may also cause sedation and pupillary changes that may obscure the clinical course of head injury
- hepatic function impairment – IBUGESIC FORTE is metabolised in the liver
- renal function impairment – IBUGESIC FORTE may cause urine retention as the metabolites are excreted via the kidneys, renal impairment may lead to accumulation resulting in an increase in adverse effects
- adrenocortical insufficiency
- inflammatory or obstructive bowel disorders – risk of toxic megacolon may be increased
- prostatic hypertrophy, obstruction, urethral stricture or recent urinary tract surgery - as urinary retention may be precipitated by IBUGESIC FORTE

- elderly or debilitated patients, these patients are more likely to develop adverse hepatic or renal effects and if gastrointestinal ulceration or bleeding occurs, it is more likely to cause serious consequences – dosage should be reduced
- alcoholism or impaired liver function – increased risk of hepatotoxicity, especially in alcoholics with high doses and prolonged use
- diabetic patients may experience false results with blood glucose tests
- surgery – possible increased risk for post-operative bleeding allergic conditions – possibility of cross sensitivity
- anaemia – may be exacerbated.

Dosages of IBUGESIC FORTE in excess of those recommended may cause severe liver damage.

This product contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or poison centre must be contacted immediately.

Risk of renal tubular acidosis and hypokalaemia are associated with non-steroidal anti-inflammatory medicine (NSAID) usage.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), eosinophilia and systemic (DRESS)/Drug-induced hypersensitivity syndrome (DIHS) and fixed drug eruptions (FDE) have been reported in patients treated with paracetamol containing

medicines. If a patient develops SCAR, treatment with IBUGESIC FORTE must immediately be discontinued and appropriate treatment instituted.

The antipyretic, analgesic and anti-inflammatory action of IBUGESIC FORTE may mask symptoms of the occurrence or worsening of infection.

IBUGESIC FORTE may cause drowsiness; ability to perform skilled tasks, drive or operate machinery may be impaired.

Avoid alcohol.

If taking for pain, including arthritic pain, and the pain persists for longer than 5 days, or if taking for fever and the fever persists for longer than 3 days, or if the condition deteriorates or new symptoms develop, the doctor needs to be contacted as additional treatment may be necessary.

4.5 Interaction with other medicines and other forms of interaction

- MAOIs – possible severe and sometimes fatal reactions may occur (see **section 4.3**).
- Alcohol or central nervous system depressants - depressant effects are enhanced.
- Anticholinergics – increased risk of severe constipation.
- Antidiarrhoeals – increased risk of severe constipation and central nervous system depression.
- Hypotension-producing medications – hypotensive effects may be potentiated.
- Hepatotoxic medicines – increased risk of hepatotoxicity.
- Enzyme inducing medicines – increased risk of hepatotoxicity. Possible decrease in therapeutic effects of paracetamol.
- Metoclopramide – absorption of paracetamol may be accelerated.
- Probenecid – excretion of paracetamol may be affected and plasma concentrations altered.
- Cholestyramine – absorption of paracetamol is reduced if given within one hour of cholestyramine.

- Anticoagulants – enhancement of anticoagulant effect and the possibility of gastrointestinal ulceration or bleeding.
- Alcohol, corticosteroids, clopidogrel, ticlopidine, bisphosphonates, oxpentifylline – increased risk of gastrointestinal bleeding and ulceration.
- Antidiabetic agents – hypoglycaemic effects of these medicines may be increased.
- Digoxin – increase in serum digoxin concentrations.
- Lithium – increase in the steady-state concentration of lithium.
- Methotrexate – increased and prolonged methotrexate plasma concentration and an increased risk of methotrexate toxicity.
- Nephrotoxic medicines e.g., ciclosporin – increased risk of nephrotoxicity.
- Antihypertensives or diuretics – reduction or reversal of the antihypertensive effect may occur.
- Bone marrow depressants – the leucopenic and/or thrombocytopenic effects of these medicines may be increased.
- Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.

4.6 Fertility, pregnancy and lactation

IBUGESIC FORTE is not recommended for use by pregnant or breastfeeding women (see **section 4.3**). Use of non-steroidal anti-inflammatory medicines during the third trimester of pregnancy, may result in persistent pulmonary hypertension of the newborn.

Use of NSAIDs, including IBUGESIC FORTE, can cause premature closure of the foetal ductus arteriosus and foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, the use of IBUGESIC FORTE dose and duration between 20 and 30 weeks of gestation should be limited and avoided at around 30 weeks of gestation and later in pregnancy (see **sections 4.3** and **4.4**).

The onset of labour may be delayed and its duration increased.

Fertility

No data on male and female fertility are available.

4.7 Effects on ability to drive and use machines

Patients should be advised not to drive or operate machinery if affected by dizziness or sedation. This medicine can impair cognitive function and can affect a patient's ability to drive safely. Patients should be advised that they do not engage in the above activities until they are aware of the measure to which IBUGESIC FORTE affects them.

4.8 Undesirable effects

Tabulated list of adverse reactions

The following adverse reactions have been classified according to the following categories, frequent, less frequent and frequency unknown.

MedDRA system organ class	**Frequency**	**Side effects**
Ibuprofen		
Blood and lymphatic system disorders	*Less frequent*:	Agranulocytosis, thrombocytopenia.
Metabolism and nutrition disorders	*Frequency unknown:*	Hypokalaemia.
Nervous system disorders	*Less frequent*:	Dizziness, nervousness, depression, drowsiness, insomnia, headache.
Eye disorders	*Less frequent:*	Blurred vision and other ocular reactions.
Cardiac disorders	*Less frequent*:	Heart failure may be precipitated in compromised patients, angina pectoris, cardiac arrhythmias.

MedDRA system organ class	Frequency	Side effects
Gastrointestinal disorders	*Frequent*:	Dyspepsia, nausea, diarrhoea, abdominal cramps and pain, bloating, constipation.
	Less frequent:	Peptic ulceration, gastrointestinal bleeding, decreased appetite.
	Frequency unknown:	Exacerbation of colitis and Crohn's disease, gastritis.
Hepato-biliary disorders	*Less frequent*:	Abnormalities of liver function tests.
Skin and subcutaneous tissue disorders	*Less frequent*:	Skin rash, pruritus.
Renal and urinary disorders	*Less frequent*:	Impairment of renal function, acute reversible renal failure, oedema.
	Frequency unknown:	Renal tubular acidosis (RTA).
Other	*Less frequent*:	Tinnitus, hypersensitivity reactions.
Paracetamol		
Blood and lymphatic system disorders	*Less frequent*:	Haematological reaction (including thrombocytopenia, leucopenia, pancytopenia, neutropenia and agranulocytosis).
Hepato-biliary	*Less frequent*:	Hepatitis.
Skin and subcutaneous tissue disorders	*Frequency unknown*:	Risk of fixed drug eruptions (FDE) and Drug-induced hypersensitivity syndrome (DIHS).

MedDRA system organ class	Frequency	Side effects
Renal and urinary disorders	*Less frequent*:	Renal colic, renal failure.
Other	*Less frequent*:	Sensitivity reactions resulting in reversible skin rash (which may be accompanied by fever and mucosal lesions) or blood disorders.
Codeine Phosphate		
Nervous system disorders	*Frequent*:	Drowsiness, confusion.
	Less frequent:	Restlessness, vertigo, changes in mood, hypothermia, raised intracranial pressure.
Eye disorders	*Less frequent*:	Changes in myosis.
Cardiac disorders	*Less frequent*:	Bradycardia, palpitations, orthostatic hypotension.
Respiratory, thoracic and mediastinal disorders	*Less frequent*:	Respiratory depression.
Gastrointestinal disorders	*Frequent*:	Nausea, vomiting, constipation.
	Less frequent:	Dry mouth.
Skin and subcutaneous tissue disorders	*Less frequent*:	Sweating, facial flushing, urticaria, pruritus.
Renal and urinary disorders	*Less frequent*:	Micturition difficulties, ureteric or biliary spasm.

Post-Marketing Experience

MedDRA system organ Class	**Frequency**	**Side effects**
Paracetamol		
Skin and subcutaneous tissue disorders	*Frequency unknown*:	Risk of fixed drug eruptions (FDE) and Drug-induced hypersensitivity syndrome (DIHS).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "Adverse drug reaction and quality problem reporting form", found online under SAHPRA's publications: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problemreporting-form/ or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

(see **section 4.8**).

Paracetamol and ibuprofen:

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person to a hospital directly. A delay in starting treatment may mean that the antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 to 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicines that induce liver

microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms of paracetamol overdose: In the first 24 hours these symptoms include pallor, nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of acute poisoning do not reflect the potential seriousness of the overdosage.

Symptoms of ibuprofen overdose: Gastrointestinal symptoms (e.g. abdominal pain, nausea, vomiting), central nervous system symptoms (e.g. lethargy, drowsiness), gastrointestinal haemorrhage, acute renal failure, convulsions and coma.

Liver damage may become apparent 12 to 48 hours, or later after ingestion of paracetamol, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentrations and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death.

Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac arrhythmias have been reported. Cerebral oedema and non-specific myocardial depression have occurred.

Treatment of overdose:

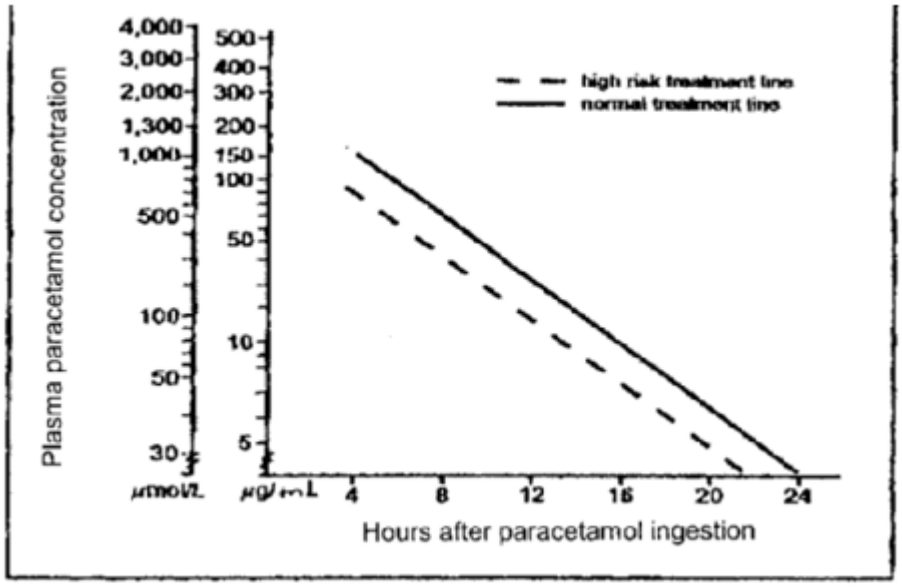
Although evidence is limited, it is recommended that an adult who has ingested 5 to 10 g or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding 4 hours, should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol

poisoning (see above). In patients who are stuperose or comatose, endotracheal intubation should precede gastric lavage in order to avoid aspiration.

N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible, preferably within 8 hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken. An initial dose of 150 mg/kg N-acetylcysteine in 200 mL dextrose injection given **intravenously** over 15 minutes, followed by an infusion of 50 mg/kg in 500 mL dextrose injection over the next 4 hours, and then 100 mg/kg in 1 000 mL dextrose injection over the next 16 hours. **The volume of intravenous fluid should be modified for children.**

Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water as a 5 % solution may be administered initially, followed by 70 mg/kg every 4 hours for seventeen doses. If activated charcoal is used, then it should be removed by gastric lavage as it may interfere with absorption of orally administered N-acetylcysteine and decrease its efficacy.

A plasma paracetamol level should be determined 4 hours after ingestion in all cases of suspected overdosage. Levels done before 4 hours, unless high, may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their 4 hours plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram. The nomogram should be used only in relation to a single acute ingestion.



Adapted from Smilkstein et al., Ann. Emerg.Med., 1991, 20, 1059

Those whose plasma paracetamol levels are above the “normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV over 16 hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “high risk treatment line”.

Prothrombin index correlates best with survival.

Monitor all patients with significant ingestions for at least 96 hours.

Codeine:

Codeine overdose may result in central nervous system and respiratory depression with hypoxia, hypotension, shock, gastric hypomotility with ileus, and non-cardiogenic pulmonary oedema. The opiate intoxication syndrome is described as a triad of depressed level of consciousness, miotic pupils, and decreased respirations.

Treatment is based more on clinical presentation than on specific laboratory data, except when complications have occurred.

Plasma codeine levels are not clinically useful.

Support the respiratory and cardiovascular function.

Monitor arterial blood gases and/or pulse oximetry, pulmonary function tests, and chest x-ray in patients with significant exposure.

Ipecac-induced emesis is not recommended because of the potential for CNS depression and seizures.

Consider pre-hospital administration of activated charcoal as aqueous slurry in patients with a potentially toxic ingestion who are awake and able to protect their airway.

Activated charcoal is most effective when administered within one hour of ingestion.

Use a minimum of 240 mL of water per 30 g charcoal.

Optimum dose has not been established, but the usual dose is 25 to 100 g in adults and adolescents; 25 to 50 g in children aged 1 to 12 years (or 0,5 to 1 g/kg body weight); and 1 g/kg in infants up to 1 year old.

Consider naloxone as antidote in patients with decreased level of consciousness. The most frequently recommended initial naloxone dose for codeine overdose is 0,4 to 2 mg intravenous bolus in both children and adults.

This dose can also be given subcutaneously in the absence of intravenous access or intratracheally.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 2.8

Pharmacotherapeutic group: Analgesic combinations

ATC code: N02AJ09

Paracetamol has analgesic and antipyretic effects. Ibuprofen has analgesic, antipyretic and anti-inflammatory activities.

Ibuprofen exerts its anti-inflammatory action peripherally in inflamed tissue by reducing prostaglandin activity and by inhibiting synthesis and/or actions of other local mediators of the inflammatory response.

Codeine is metabolised to morphine, which in turn, exerts an analgesic effect.

5.2 Pharmacokinetic properties

Paracetamol:

Absorption following oral administration is rapid and almost complete. Paracetamol is metabolised in the liver primarily by conjugation. Paracetamol has a half-life of 1 to 4 hours, time to peak concentration of 0,5 to 2 hours, time to peak effect of 1 to 3 hours and the duration of action of 3 to 4 hours. Paracetamol is renally excreted primarily as metabolites and 3 % of a dose may be excreted unchanged.

Ibuprofen:

Rapidly absorbed after oral administration. Onset of action for pain relief is 30 minutes and the time for peak effect for fever is 2 to 4 hours. The half-life of ibuprofen is about 2 hours and the duration of action for fever is 6 to 8 hours or more and is 4 to 6 hours for pain. More than 90 % of an ingested dose is excreted in the urine as metabolites or their conjugates.

Codeine:

Readily absorbed from the gastrointestinal tract. Half-life is 2,5 to 4 hours. Codeine is metabolised in the liver. The cytochrome P450 enzyme 2D6 converts codeine to morphine, one of its metabolites. About 10 % of the dose is demethylated to morphine. Onset of action is 30 to 45 minutes. The time to peak effect is 1 to 2 hours. Duration of action is 4 hours. Codeine is eliminated via the kidneys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill

Microcrystalline cellulose

Pregelatinised starch

Purified talc

Capsule shell

Capsule body (red)

Erythrosine

Gelatin

Red iron oxide

Titanium dioxide

Yellow iron oxide

Capsule cap (dark green)

Indigo carmine

Gelatin

Quinoline yellow

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Amber glass bottles: 36 months

PP securitainers: 36 months

PVC and Tristar blisters: 24 months (3.2.P.8.1)

Patient ready packs: 24 months

6.4 Special precautions for storage

Securitainer and amber glass bottle: Keep well closed and store at or below 25 °C.

Blister strips and patient ready packs: Keep in outer carton until required for use. Store at or below 25 °C.

Protect from light.

6.5 Nature and contents of container

White opaque securitainers with 10 or 30 capsules.

Clear PVC or Tristar blisters sealed with aluminium foil with 30 capsules packed into a cardboard carton.

Sealed aluminium bags with 30 capsules.

Amber glass bottles with 30 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER

37/2.8/0135

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorization: 03 June 2005

Latest renewal: To be allocated.

10. DATE OF REVISION OF THE TEXT

15 October 2024