Applicant:	**ADCOCK INGRAM LIMITED**
Product Name:	**PANADO PLUS**
Dosage form and strength:	200 mg Ibuprofen and 250 mg Paracetamol per capsule.

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

PANADO® PLUS capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **PANADO® PLUS** capsule contains:

Ibuprofen 200 mg

Paracetamol 250 mg

Sugar free.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsules

A hard gelatin capsule with opaque, white body and cap, containing a white, granular powder. 'PANADO PLUS' is printed in red ink on the capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PANADO® PLUS is indicated for the relief of headache from musculo-skeletal origin, feverishness, muscular, menstrual and dental pain.

4.2 Posology and method of administration received

DO NOT EXCEED THE RECOMMENDED DOSE

Not recommended for children under twelve years.

Adults and children over 12 years:

Two capsules every four hours, but not more than six capsules in twenty four hours. Capsules are to be taken with food or after meals with sufficient water. Maximum treatment period 10 days.

Consult your doctor if no relief is obtained with the recommended dosage.

Use the lowest effective dose for the shortest possible duration of treatment.

4.3 Contraindications

PANADO® PLUS capsules should not be given to patients with:

- Heart failure
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including **PANADO® PLUS**.
- Active or history of recurrent ulcer/haemorrhage/perforations.
- **PANADO® PLUS** capsules should not be given to patients with asthma or bronchospasm, bleeding disorders, cardiovascular disease, peptic ulceration or a history of such ulceration, renal failure and in those who are receiving coumarin anticoagulants
- **PANADO® PLUS** capsules are contraindicated in patients with a history of hypersensitivity reactions to aspirin or other NSAID's, including those in whom attacks of asthma, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAIDs.
- Severe liver function impairment.
- Patients who are hypersensitive to any of the ingredients of **PANADO® PLUS** or aspirin should not be given **PANADO® PLUS** capsules.
- Avoid use of NSAIDS 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.

4.4 Special warnings and precautions for use:

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.

- Dosages in excess of those recommended may cause severe liver damage
- **PANADO® PLUS** capsules are not recommended for use by pregnant or breast-feeding women. Regular use of NSAID's during the third trimester of pregnancy may result in premature closure of the foetal ductus arteriosis in utero and possibly in persistent pulmonary hypertension of the newborn. The onset of labour may be delayed and its duration increased.
- Patients suffering from liver or kidney disease should only take **PANADO® PLUS** under medical supervision.
- Do not use continuously for more than ten days without consulting your doctor.
- Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with **PANADO® PLUS** therapy. In view of the **PANADO® PLUS**'s inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.
- Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs including **PANADO® PLUS**, especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.
- The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of **PANADO® PLUS**, in patients with a history of ulcers, and the elderly.
- When gastrointestinal bleeding or ulceration occurs in patients receiving **PANADO® PLUS**, treatment with **PANADO® PLUS** should be stopped.
- **PANADO® PLUS** should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

- Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. **PANADO® PLUS** should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
- Should be used with caution in patients with infection since symptoms such as fever and inflammation may be masked.
- Foetal Toxicity: Limit use of NSAIDs, including **PANADO® PLUS**, between 20 and 30 weeks of pregnancy due to the risk of oligohydramnios/foetal renal dysfunction. Avoid use of NSAIDs 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.
- If NSAID treatment is necessary between 20 and 30 weeks gestation, limit **PANADO® PLUS** use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if **PANADO® PLUS** treatment extends beyond 48 hours. Discontinue **PANADO® PLUS** if oligohydramnios occurs and follow up according to clinical practice.

4.5 Interaction with other medicines and other forms of interaction

- Anticoagulants: Notable interactions involving NSAID's include enhancement of the effects of oral anticoagulants (especially by azapropazone and phenylbutazone).
- Lithium: Increased plasma concentrations of lithium
- Methotrexate: Increased plasma concentrations of methotrexate
- Cardiac glycosides: Increased plasma concentrations of cardiac glycosides.
- ACE inhibitors and diuretics: The risk of nephrotoxicity may be increased if given with ACE inhibitors, or diuretics. Effects on renal function may lead to reduced excretion of some drugs. There may also be an increased risk of hyperkalaemia with ACE inhibitors and potassium-sparing diuretics.
- Ciclosporin: The risk of nephrotoxicity may be increased if given with ciclosporin.
- Tacrolimus: The risk of nephrotoxicity may be increased if given with tacrolimus.

- Antihypertensives: The antihypertensive effects of some antihypertensives including ACE inhibitors, beta blockers, and diuretics may be reduced.
- Quinolines: Convulsions may occur due to an interaction with quinolones.
- Phenytoin: NSAID's may enhance the effects of phenytoin.
- Sulphonylurea antidiabetics: NSAID's may enhance the effects of sulphonylurea antidiabetics.
- Moclobemide: The effects of NSAID's might be enhanced by use with moclobemide.
- NSAIDs: use of two or more NSAIDs concomitantly could result in an increase in side effects.
- Corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).
- Alcohol: The risk of gastrointestinal bleeding and ulceration associated with NSAID's is increased when used with alcohol.
- Bisphosphonates: The risk of gastrointestinal bleeding and ulceration associated with NSAID's is increased when used with bisphosphonates.
- Oxypentifylline: The risk of gastrointestinal bleeding and ulceration associated with NSAID's is increased when used with oxypentifylline.
- Zidovudine: There may be an increased risk of haemotoxicity during concomitant use of zidovudine and NSAID's; blood counts 1 to 2 weeks after starting use together are recommended.
- Mifepristone: The manufacturer of mifepristone advises that NSAID's or aspirin should be avoided for 8 to 12 days after mifepristone use because of a theoretical risk that these prostaglandin synthetase inhibitors may alter the efficacy of mifepristone.
- Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.

4.6 Fertility, pregnancy and lactation

PANADO® PLUS capsules are not recommended for use by pregnant or breast-feeding women (see section 4.4).

Use of NSAIDs, including **PANADO® PLUS**, 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 **PANADO® PLUS** 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 section 4.3 and 4.4).

Fertility

No data available

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery (see section 4.8).

4.8 Undesirable effects

Ibuprofen:

System Organ Class	Adverse Event	Frequency
Cardiac disorders	Oedema, hypertension and cardiac failure	Frequency unknown
Gastrointestinal disorders	The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis.	Frequent

Skin and subcutaneous tissue disorders	Bullous reactions, including Stevens-Johnson syndrome, and toxic epidermal necrolysis, skin rash, pruritis	Frequency unknown
Nervous system disorders	Headache, dizziness, nervousness, drowsiness, insomnia, aseptic meningitis	Frequency unknown
Ear and labyrinth disorders	Vertigo and tinnitus	Frequency unknown
Psychiatric disorders	Depression	Frequency unknown
Eye disorders	Blurred vision and other ocular reactions	Frequency unknown
Immune system disorders	Sensitivity reactions, fever, angioedema, bronchospasm and rashes	Frequency unknown
Hepato-biliary disorders	Hepatotoxicity, hepatitis and liver failure	Less frequent
Investigations	Abnormalities of liver function tests	Frequency unknown
Renal and urinary disorders	Impairment of renal function and acute reversible renal failure. Increase in serum creatinine concentration, nephrotic syndrome. Cystitis, haematuria, and interstitial nephritis may occur.	Frequency unknown
Blood and lymphatic system disorders	Agranulocytosis, anaemias, neutropaenia, eosinophilia, and thrombocytopaenia have been observed. Reversible inhibition of platelet aggregation may occur.	Frequency unknown

Paracetamol:

System Organ Class	Adverse Event	Frequency
Blood and lymphatic system disorders	Haematological reactions including thrombocytopaenia, leucopaenia, pancytopaenia, neutropaenia, and agranulocytosis have been reported	Less frequent
Endocrine disorders	Pancreatitis	Frequency unknown
Immune system disorders	Skin rashes and other hypersensitivity reactions may occur. The rash is usually erythematous or urticarial but sometimes more serious and accompanied by fever and mucosal lesions	Frequency unknown
Skin reactions and subcutaneous tissue disorders	Stevens-Johnson syndrome, toxic epidermal necrolysis acute generalised exanthematous pustulosis have been reported. More mild rashes and other hypersensitivity reactions also occur occasionally.	Less frequent
Metabolism and nutrition disorders	Pyroglutamic aciduria (5-oxoprolinuria) and high-anion gap metabolic acidosis	Frequency unknown
General disorders and administrative site conditions	Hypersensitivity reactions characterised by urticaria, dyspnoea, and hypotension have occurred. Angioedema has also been reported.	Frequency unknown

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 provders are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Ibuprofen:

The most likely symptoms of overdosage are nausea, vomiting and tinnitus. Treatment is symptomatic and supportive.

Paracetamol:

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person directly to a hospital. 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 -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 overdosage in the first 24 hours 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.

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

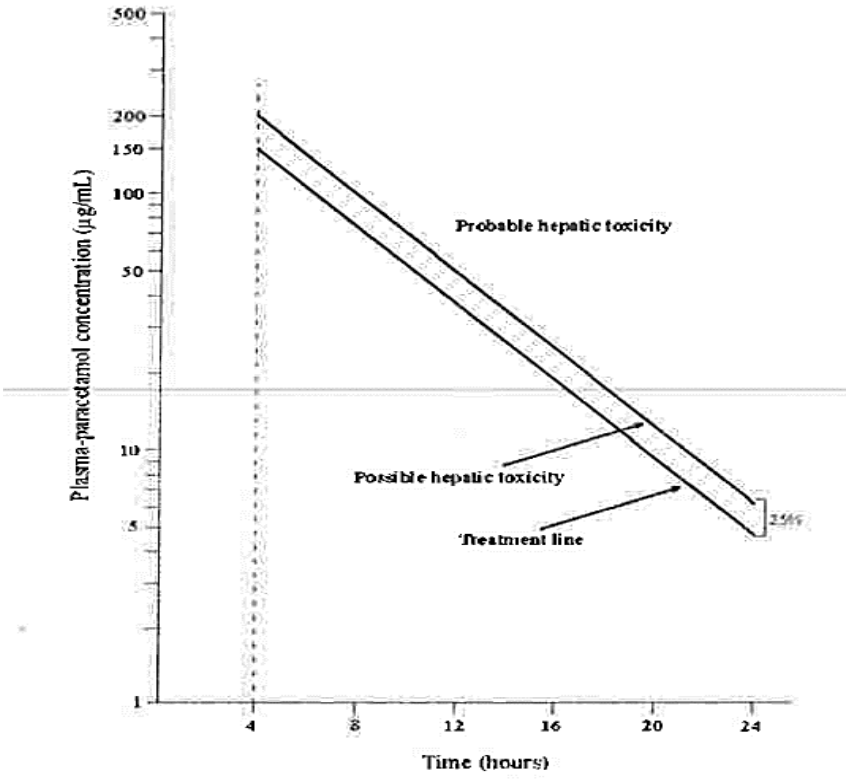
Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac arrhythmias have been reported.

Treatment for paracetamol overdosage:

Although evidence is limited it is recommended that any adult person who has ingested 5 - 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four 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 eight 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 four hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next sixteen 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 may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.
A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their 4-hour plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.



Source: Martindale: The Complete Drug Reference -37th Edition.

Those whose plasma paracetamol levels are above the “normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen 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 ninety six hours.

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.8 Analgesic combinations

5.2 Pharmacokinetic properties

No data available

5.3 Preclinical safety

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Product Name:	**PANADO PLUS**
Dosage form and strength:	200 mg Ibuprofen and 250 mg Paracetamol per capsule.

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinized starch

Microcrystalline cellulose

Sodium stearyl fumarate

Gelatin

Titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ^{o}C in a well-closed container, protected from light.

6.5 Nature and contents of container

Securitainers with 30 or 60 capsules; tracer packs with 20 or 60 capsules; blister pack with 20 or 100 capsules.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Adcock Ingram Limited

1 New Road, Erand Gardens,

Midrand, 1685

Private Bag X69, Bryanston, 2021

8. REGISTRATION NUMBER

35/2.8/0070

BOTSWANA REGISTRATION NUMBER:

30's in HDPE	BOT1502723 S3
60's in HDPE	BOT1502723A S3
20's in PP Tracer pack	BOT1502723B S3
60's in PP Tracer pack	BOT1502723C S3
100's in blister pack	BOT1502723D S3

NAMIBIA REGISTRATION NUMBER:

NS1 12/2.8/0247

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 September 2002

10. DATE OF REVISION OF THE TEXT

25/03/2022