SUMMARY OF PRODUCT CHARACTERISTICS
BRUPAL KID (Ibuprofen 100 mg and Paracetamol 125 mg Uncoated Tablets)

1. NAME OF THE MEDICINAL PRODUCT

BRUPAL KID (Ibuprofen and Paracetamol Uncoated Tablets)

Commercial name: BRUPAL KID

INN or generic name: Ibuprofen and Paracetamol Tablets

Strength: Each uncoated tablet contains Ibuprofen BP 100 mg and Paracetamol BP 125 mg.

Pharmaceutical form: Uncoated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains the following active ingredients:

Ibuprofen BP – 100 mg

Paracetamol BP – 125 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Uncoated tablet.

Pale yellow, flat, circular, uncoated tablets with a breakline on one side and plain on the other side, packed in an aluminium strip.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

BRUPAL KID is indicated for the relief of mild to moderate pain associated with inflammation.

4.2 Posology and Method of Administration

Posology

Always take BRUPAL KID 100 mg/125 mg tablets as prescribed by the doctor. Do not consume more than the prescribed dose. Take this medicine after food to reduce the chances of stomach upset. Side effects such as sleepiness/drowsiness are common.

Not recommended for children under twelve years of age.

Method of administration

Oral route of administration.

4.3 Contraindications

BRUPAL KID is contraindicated in patients with the following conditions:

History of severe allergic reaction such as anaphylaxis or angioedema, induced by aspirin or other NSAIDs. Because of the possibility of cross-sensitivity due to structural relationships which exist among non-steroidal anti-inflammatory medicines, acute allergic reactions are likely to occur in patients who have exhibited allergic reactions to these compounds.

Patients sensitive to any of the ingredients.

4.4 Special Warnings and Precautions for Use

Dosages in excess of those recommended may cause severe liver function damage. Patients suffering from liver or kidney disease should take paracetamol under medical supervision. Consult a doctor if no relief is obtained from the recommended dosage. Do not use continuously for more than 10 days without consulting a doctor.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Drug-drug interactions

Ibuprofen drug interactions

A. Acenocoumarol

Summary: Studies evaluating doses of ibuprofen as high as 2.4 grams per day have not demonstrated that the drug affects the hypoprothrombinemic response to warfarin or other anticoagulants. Therefore, ibuprofen may be one of the safer NSAIDs to use in patients requiring oral anticoagulant therapy (Boekhout-Mussert & Loeliger, 1974; Thilo et al, 1974; Penner & Abbrecht, 1975). However, since ibuprofen can inhibit platelet aggregation and cause gastric erosion, caution should be used when ibuprofen is administered with any coumarin-type anticoagulant.

Adverse effect: An increased risk of bleeding.

Clinical management: In patients receiving oral anticoagulation, the prothrombin time (PT) or international normalized ratio (INR) should be closely monitored with the addition and withdrawal of treatment with non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen. Coagulation parameters should also be reassessed periodically during concurrent therapy. Adjustments of the acenocoumarol dose may be necessary in order to maintain the desired level of anticoagulation. Clinicians and patients should be aware of the increased potential for bleeding, especially from the gastrointestinal tract, during concomitant therapy.

B. Paracetamol

Summary: At steady state, the pharmacokinetics of paracetamol and ibuprofen are not changed when administered concurrently (Wright et al, 1983).

Severity: None.

Onset: Not specified.

Documentation: Poor.

C. Alendronate

Summary: During a three-year controlled clinical study involving 2027 patients in which the majority of patients were receiving non-steroidal anti-inflammatory agents (NSAIDs), the incidence of upper gastrointestinal adverse effects was similar between patients receiving alendronate and patients receiving placebo. Therefore, alendronate may be administered to patients receiving NSAID therapy. However, because both NSAID and alendronate use has been associated with gastrointestinal irritation, caution should be exercised with concomitant administration.

Severity: Minor.

Onset: Delayed.

Documentation: Fair.

D. Angiotensin converting enzyme inhibitors

Summary: NSAIDs may decrease the antihypertensive and natriuretic effect of ACE inhibitors, particularly in low renin hypertensive patients (Morgan & Anderson, 1993; Sturrock & Struthers, 1993). The mechanism may involve attenuation of the effectiveness of antihypertensive agents secondary to interference with production of vasodilator and natriuretic prostaglandins that are stimulated by antihypertensive agents. While there are no known significant pharmacokinetic interactions between NSAIDs and ACE inhibitors (Shionoiri, 1993), the combination of NSAIDs and ACE inhibitors can produce side effects such as marked bradycardia due to hyperkalemia. This can further lead to syncope in which the peaked T wave is induced. Aged patients suffering from hypertension, diabetes mellitus, ischemic heart disease and degenerative joint disease must be careful when taking these medications in combination (Kurata et al, 1999). Elevated blood pressure was observed in a patient when rofecoxib was added to lisinopril (Brown, 2000).

Adverse effect: Decreased antihypertensive and natriuretic effects.

Clinical management: Caution is advised if a non-steroidal anti-inflammatory agent (NSAID) is co-administered with an angiotensin converting enzyme (ACE) inhibitor, especially in patients predisposed to or with preexisting nephropathy. Monitor blood pressure and cardiovascular function for a reduction in the efficacy of the ACE inhibitor. Also monitor the patient for hyperkalemia or acute renal failure.

Severity: Minor.

Onset: Delayed.

Documentation: Fair.

Probable mechanism: Interference with production of vasodilator and natriuretic prostaglandins.

E. Antipyrine

Summary: Ibuprofen does not appear to impair antipyrine clearance (Abernethy & Greenblatt, 1983). Ibuprofen is unlikely to impair clearance of drugs metabolized via microsomal oxidation.

Severity: None.

Onset: Not specified.

Documentation: Poor.

F. Anisindione

Summary: Studies evaluating doses of ibuprofen as high as 2.4 grams per day have not demonstrated that the drug affects the hypoprothrombinemic response to warfarin or other anticoagulants. Therefore, ibuprofen may be one of the safer NSAIDs to use in patients requiring oral anticoagulant therapy (Boekhout-Mussert & Loeliger, 1974; Thilo et al, 1974; Penner & Abbrecht, 1975). However, since ibuprofen can inhibit platelet aggregation and cause gastric erosion, caution should be used when ibuprofen is administered with any coumarin-type anticoagulant.

Adverse effect: An increased risk of bleeding.

Clinical management: In patients receiving oral anticoagulation, the prothrombin time (PT) or international normalized ratio (INR) should be closely monitored with the addition and withdrawal of treatment with non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen. Coagulation parameters should also be reassessed periodically during concurrent therapy. Adjustments of the anisindione dose may be necessary in order to maintain the desired level of anticoagulation. Clinicians and patients should be aware of the increased potential for bleeding, especially from the gastrointestinal tract, during concomitant therapy.

Severity: Moderate.

Onset: Delayed.

Documentation: Poor.

Probable mechanism: Gastric erosion, inhibition of platelet function.

G. Antacids

Summary: Concomitant administration of antacids (oral Maalox® 400 mg) and ibuprofen was reported to result in no alterations in the pharmacokinetics of ibuprofen (Gontarz et al, 1987).

Severity: None.

Onset: Not specified.

Documentation: Fair.

H. Aspirin

Summary: Ibuprofen reduced the antiplatelet effect of aspirin in healthy subjects and increased the risk of all-cause mortality in patients with cardiovascular disease taking aspirin for cardioprotection (MacDonald & Wei, 2003; Catella-Lawson et al, 2001).

Adverse effect: Decreased antiplatelet effect of aspirin.

Clinical management: In patients taking daily aspirin for cardioprotective effects who use ibuprofen occasionally, aspirin should be taken at least 2 hours before the ibuprofen. If the patient is on chronic ibuprofen therapy, switching to paracetamol, a different NSAID, or a COX-2 inhibitor is recommended.

I. Beta-adrenergic blockers

Summary: The concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) and beta-adrenergic blockers has been reported to result in increases in blood pressure and interference with blood pressure control. This effect has been reported for flurbiprofen (400 mg daily), ibuprofen (more than 400 mg daily), indomethacin (more than 50 mg daily), naproxen (1000 mg daily) and piroxicam (Radack et al, 1987; Webster et al, 1984; Abate et al, 1990; Chalmers et al, 1984; Durao et al, 1977; Salvetti et al, 1984; Watkins et al, 1980). A number of studies suggest sulindac may not antagonize the antihypertensive effects of beta blockers (Abate et al, 1991; Ebel et al, 1986; Mills et al, 1982; Salvetti et al, 1984; Durao et al, 1977).

Adverse effect: Decreased antihypertensive effect.

Clinical management: If concurrent therapy is required, monitor the patient's blood pressure carefully and assess the need for a dosage adjustment for the beta blocker.

Severity: Minor.

Onset: Delayed.

Documentation: Fair.

Probable mechanism: Decreased production of vasodilating and renal prostaglandins.

J. Beta glucan

Summary: Co-administration of beta glucan and several NSAIDs resulted in lethal gastrointestinal damage in mice (Takahashi et al, 2001). The mechanism of the interaction may involve enteric-induced bacterial peritonitis (Takahashi et al, 2001) or possibly alteration of the cytokine network resulting in acute inflammation (Yoshioka et al, 1998).

Adverse effect: Severe gastrointestinal damage.

Clinical management: The clinical significance of this interaction observed in animals is not known. Concomitant use of therapeutic doses of beta glucan and NSAIDs is not recommended.

Severity: Major.

Onset: Rapid.

Documentation: Poor.

Probable mechanism: Enteric-induced bacterial peritonitis; possibly alteration of the cytokine network resulting in acute inflammation.

K. Calcium channel blockers

Summary: Calcium channel blockers may be associated with an increased risk of gastrointestinal haemorrhage (Pahor et al, 1996). This single observational study has yet to be confirmed, but caution is warranted in combinations of calcium channel blockers and other drugs that are known to increase the risk of bleeding, such as non-steroidal anti-inflammatory agents (NSAIDs). Studies have been conflicting regarding any pharmacokinetic interactions between calcium channel blockers and NSAIDs (Pancera et al, 1996; Harvey et al, 1995; Minuz et al, 1995; Houston et al, 1995; Klassen et al, 1995; Muck et al, 1995; Polonia et al, 1995). NSAIDs have been shown to antagonize most antihypertensive drug classes (Wong et al, 1986).

Adverse effect: An increased risk of gastrointestinal haemorrhage and/or antagonism of hypotensive effect.

Clinical management: Caution is advised if NSAIDs and calcium channel blockers are used concomitantly. Monitor for signs and symptoms of gastrointestinal haemorrhage, such as weakness, nausea and blood in the stool. The antihypertensive effects of calcium channel blockers may be antagonized by concomitant administration of NSAIDs.

Severity: Minor.

Onset: Delayed.

Documentation: Fair.

Probable mechanism: Additive effects.

L. Chaparral

Summary: There have been more than 13 cases of chaparral-induced hepatotoxicity reported (Grant et al, 1998; Sheikh et al, 1997; Batchelor et al, 1995; Gordon et al, 1995; Alderman et al, 1994; Smith & Desmond, 1993; Anon, 1992; Katz & Saibil, 1990). Theoretically, consuming chaparral with other hepatotoxic drugs and herbs could increase the likelihood of hepatitis, jaundice or hepatic veno-occlusive disease. Consumption of hepatotoxic herbs has been associated with hepatic veno-occlusive disease and death, including one neonatal death after intrauterine exposure following maternal consumption of herbal teas during pregnancy (Huxtable, 1992). Similarly, chaparral should not be combined with other herbs with the potential to cause hepatotoxicity. These include but are not limited to chaparral (Larrea tridentata), Russian comfrey (Symphytum x uplandicum), coltsfoot (Tussilago farfara), germander (Teucrium chamaedrys), jin bu huan, pennyroyal (Mentha pulegium, Hedeoma pulegoides), petasites (Petasites japonicus), Senecio longilobus (groundsel), Scutellaria laterifolia (skullcap), Heliotropium spp., Crotolaria spp., Phoradendron and Viscum sp. (mistletoe) and Cassia acutifolia (senna) (Huxtable, 1992). Symphytum, Senecio, Crotolaria and Heliotropium sp. contain pyrrolizidine alkaloids.

Adverse effect: Elevated liver transaminases with or without concomitant hepatic damage.

Clinical management: Avoid use of chaparral while taking drugs with potential for hepatotoxicity. For those patients who elect to use chaparral despite this advice, liver function tests should be monitored closely.

Severity: Major.

Onset: Delayed.

Documentation: Fair.

Probable mechanism: Unknown.

M. Cimetidine

Severity: None.

Onset: Not specified.

Documentation: Poor.

N. Clonidine

Summary: Concomitant therapy with ibuprofen and antihypertensive agents has been reported to result in increases in blood pressure and interference with blood pressure control (Radack et al, 1987). In this study, paracetamol had no demonstrable effect upon blood pressure when given with antihypertensive agents. Ibuprofen was given in doses of 400 mg orally every eight hours to hypertensive patients receiving their usual medications (primarily diuretics with beta-blockers, centrally-acting adrenergic antagonists or vasodilators). This study supports previous data demonstrating increases in blood pressure with non-steroidal anti-inflammatory agents. The mechanism may involve attenuation of the effectiveness of antihypertensive agents secondary to interference with production of vasodilator and antiuretic prostaglandins that are stimulated by antihypertensive agents. However, a reduction in sodium excretion may have been involved in exacerbating hypertension. More studies are required to fully evaluate the mechanisms of this interaction. Since the doses utilized in this study were consistent with recommended over-the-counter doses of ibuprofen, it is suggested that blood pressure monitoring be undertaken more frequently and that greater caution be exercised when treating patients with hypertension who are also receiving non-prescription ibuprofen.

Severity: Not specified.

Onset: Not specified.

Documentation: Poor.

O. Clopidogrel

Summary: In healthy volunteers receiving naproxen, concomitant administration of clopidogrel was associated with increased occult gastrointestinal blood loss. The co-administration of NSAIDs and clopidogrel should be undertaken with caution.

Adverse effect: An increased risk of bleeding.

Clinical management: Patients receiving clopidogrel and a non-steroidal anti-inflammatory agent (NSAID) concurrently should be monitored closely for

bleeding. Gastrointestinal bleeding is a particular concern with this combination. Clopidogrel and NSAIDs should be co-administered with caution.

Severity: Moderate.

Onset: Delayed.

Documentation: Fair.

Probable mechanism: Decreased platelet function; decreased coagulation.

P. Comfrey

Summary: Comfrey has demonstrated hepatotoxicity in humans and animals. The United States Food and Drug Administration (FDA) has requested that all products containing comfrey be removed from the market (Lewis, 2001). If given with a drug with the potential to exert hepatotoxic effects, the patient may be placed at increased risk for liver injury. Similarly, comfrey should not be combined with other herbs with the potential to cause hepatotoxicity. These include but are not limited to chaparral (Larrea tridentata), Russian comfrey (Symphytum x uplandicum), coltsfoot (Tussilago farfara), germander (Teucrium chamaedrys), jin bu huan, pennyroyal (Mentha pulegium, Hedeoma pulegoides) and petasites (Petasites japonicus) (Smith & Culvenor, 1981). The toxicity of comfrey is presumed to be secondary to its pyrrolizidine alkaloid content. These alkaloids are activated in the liver to pyrrolic dehydro-alkaloids which are reactive alkylating agents thought to be responsible for liver cell necrosis (Winship, 1991; Smith & Culvenor, 1981). The metabolites have been identified as highly reactive dihydropyrrolizine esters which, when released in the liver, react with nucleophilic tissue leading to liver damage (Mattocks, 1970). Chronic use may result in selective interference with parenchymal cell function which can be sustained for periods of weeks without loss of cell viability (Culvenor et al, 1980). However, one study of liver function in chronic comfrey users showed no significant changes in bilirubin, AST or GGT levels (Anderson & McLean, 1989).

Adverse effect: Elevated liver transaminases with or without concomitant hepatic damage.

Clinical management: Comfrey is a known hepatotoxin and should be avoided.

Severity: Major.

Onset: Rapid.

Documentation: Fair.

Probable mechanism: Pyrrolizidine alkaloids in comfrey are activated in the liver to pyrrolic dehydro-alkaloids which are reactive alkylating agents thought to be responsible for liver cell necrosis.

<u>Paracetamol drug interactions</u>

A. Acenocoumarol

Summary: The anticoagulant effect of acenocoumarol may be potentiated by paracetamol administration. A 72-year-old male stabilized on acenocoumarol 2 mg daily began self-medicating with paracetamol 1 to 2 grams daily for lower

back pain. The consistency of paracetamol dosing is not known, but his International Normalized Ratio (INR) values remained stable with an average INR of 2.46. Approximately two weeks after discontinuing paracetamol, his INR decreased to 1.62. One week later the INR was 1.67. The patient restarted paracetamol 1 g daily and his INR increased to 2.02 within a week (Bagheri et al, 1999).

Adverse effect: Potentiation of anticoagulant effect.

Clinical management: Patients receiving acenocoumarol should be cautioned to limit their intake of paracetamol; a prudent rule of thumb would be to use no more than 2 grams of paracetamol per day for no more than a few days. Patients needing to take larger doses of paracetamol (or for longer periods) should have intensified monitoring of prothrombin times in order to assess any effect on anticoagulant response.

Severity: Moderate.

Onset: Delayed.

Documentation: Poor.

Probable mechanism: Inhibition of acenocoumarol metabolism or interference with clotting factor formation.

B. Amantadine

Summary: Five healthy adults participated in a study to determine the influence of amantadine on the pharmacokinetics of itself and paracetamol. Subjects ingested amantadine 200 mg daily for 42 days and then received paracetamol 650 mg as a single dose. After a two-week washout period, the same subjects received a single dose of amantadine 200 mg, followed by a single dose of paracetamol 650 mg twelve hours later. Pharmacokinetic parameters after 42 days of amantadine ingestion were not different than after the single dose of amantadine, indicating that amantadine does not induce its own metabolism. The paracetamol pharmacokinetic data were not altered by the acute or chronic administration of amantadine. The authors concluded that no dosing change in either drug is required when paracetamol and amantadine are co-administered (Aoki & Sitar, 1992).

Severity: None.

Onset: Not specified.

Documentation: Poor.

C. Antacids

Summary: Albin et al (1985) administered paracetamol and antacids to twelve healthy volunteers in a random cross-over design to determine the effect of two antacid formulations on the bioavailability of paracetamol. Subjects received the following three treatments in random order, all separated by one week: paracetamol 500 mg; paracetamol 500 mg with 15 mL of an antacid containing aluminium hydroxide, magnesium hydroxide and dimethicone gel; and paracetamol 500 mg with 15 mL of an antacid containing aluminium and

magnesium hydroxide gel. The time to maximum paracetamol concentration was significantly delayed by the administration of antacid (0.85 hr vs. 1.43 hr and 1.25 hr), but the mean plasma peak and maximum plasma concentration of paracetamol did not differ between the treatment phases. Concurrent administration of paracetamol and antacid also did not alter the elimination half-life of paracetamol (2.35 hr vs. 2.32 hr and 2.36 hr). The authors concluded that the delayed absorption of paracetamol would not have significance in a clinical setting.

Severity: None.

Onset: Not specified.

Documentation: Poor.

D. Atenolol

Severity: None.

Onset: Not specified.

Documentation: Poor.

E. Busulfan

Summary: Paracetamol decreases glutathione levels in the blood and tissues, and busulfan is eliminated from the body via conjugation with glutathione. Therefore, use of paracetamol less than 72 hours before or concurrently with busulfan may result in reduced busulfan clearance. The clinical significance of this interaction is not yet known.

Adverse effect: Reduced busulfan clearance.

Clinical management: Until the clinical significance of this interaction is further defined, paracetamol use should be minimized or eliminated less than 72 hours before the administration of busulfan.

Severity: Moderate.

Onset: Delayed.

Documentation: Fair.

Probable mechanism: Decreased glutathione available for conjugation.

F. Cabbage

Summary: Cabbage increased the metabolism of paracetamol in humans, which was suggested to be due to enhanced glucuronidation (Pantuck et al, 1984). This may result in decreased clinical effectiveness of paracetamol.

Adverse effect: Decreased paracetamol effectiveness.

Clinical management: Use caution if cabbage is used concomitantly with paracetamol.

Severity: Moderate.

Onset: Rapid.

Documentation: Fair.

Probable mechanism: Cabbage may enhance the glucuronidation of paracetamol to inactive metabolites.

G. Captopril

Severity: None.

Onset: Not specified.

Documentation: Poor.

H. Carbamazepine

Summary: The hepatotoxicity of paracetamol may be related to the formation of toxic metabolites in the liver. When carbamazepine, an enzyme inducer, is given concurrently with high and frequent doses of paracetamol, the induction of the metabolism of paracetamol may result in an increased level of hepatotoxic metabolites. In support of this theory, it has been observed that patients who receive enzyme-inducing agents do not recover as well from a paracetamol overdose as patients who are not taking enzyme-inducing drugs. The significance of this interaction at therapeutic doses of paracetamol administered intermittently appears low. In addition, paracetamol has been shown to have lower bioavailability in epileptic patients receiving enzyme-inducing agents (Perucca & Richens, 1979).

Adverse effect: An increased risk of paracetamol hepatotoxicity.

Clinical management: At usual therapeutic oral doses of carbamazepine and paracetamol, no special monitoring is required.

Severity: Moderate.

Onset: Delayed.

Documentation: Poor.

Probable mechanism: Increased metabolism of paracetamol resulting in abnormally high levels of hepatotoxic metabolites.

I. Chaparral

Summary: There have been more than 13 cases of chaparral-induced hepatotoxicity reported (Grant et al, 1998; Sheikh et al, 1997; Batchelor et al, 1995; Gordon et al, 1995; Alderman et al, 1994; Smith & Desmond, 1993; Anon, 1992; Katz & Saibil, 1990). Theoretically, consuming chaparral with other hepatotoxic drugs and herbs could increase the likelihood of hepatitis, jaundice or hepatic veno-occlusive disease. Consumption of hepatotoxic herbs has been associated with hepatic veno-occlusive disease and death, including one neonatal death after intrauterine exposure following maternal consumption of herbal teas during pregnancy (Huxtable, 1992). Similarly, chaparral should not be combined with other herbs with the potential to cause hepatotoxicity. These include but are not limited to chaparral (Larrea tridentata), Russian comfrey (Symphytum x uplandicum), coltsfoot (Tussilago farfara), germander (Teucrium chamaedrys), jin bu huan, pennyroyal (Mentha pulegium, Hedeoma pulegoides), petasites (Petasites japonicus), Senecio longilobus (groundsel), Scutellaria laterifolia (skullcap), Heliotropium spp., Crotolaria spp., Phoradendron and

Viscum sp. (mistletoe) and Cassia acutifolia (senna) (Huxtable, 1992). Symphytum, Senecio, Crotolaria and Heliotropium sp. contain pyrrolizidine alkaloids.

Adverse effect: Elevated liver transaminases with or without concomitant hepatic damage.

Clinical management: Avoid use of chaparral while taking drugs with potential for hepatotoxicity. For those patients who elect to use chaparral despite this advice, liver function tests should be monitored closely.

Severity: Major.

Onset: Delayed.

J. Chloramphenicol

Summary: Concomitant use of paracetamol (greater than or equal to 1 g four times daily) and chloramphenicol (greater than or equal to 500 mg every six hours) has been reported to increase, decrease and have no change on the chloramphenicol half-life (Stein et al, 1989).

Adverse effect: Chloramphenicol toxicity (vomiting, hypotension, hypothermia).

Clinical management: Monitor chloramphenicol concentrations and adjust dosage of chloramphenicol as necessary.

Severity: Minor.

Onset: Delayed.

Documentation: Poor.

Probable mechanism: Unknown.

K. Cholestyramine

Summary: In a controlled study the concurrent use of cholestyramine and paracetamol resulted in significantly lower plasma levels when compared to paracetamol given alone (Dordoni et al, 1973).

Adverse effect: Decreased paracetamol effectiveness.

Clinical management: If both drugs are required, give paracetamol one hour prior to or three to four hours after cholestyramine.

Severity: Minor.

Onset: Rapid.

4.6 Fertility, Pregnancy and Lactation

Paracetamol

U.S. Food and Drug Administration's Pregnancy Category B (Briggs et al, 1994).

Australian Drug Evaluation Committee's (ADEC) Category A (ADEC, 1996).

Although therapeutic doses of paracetamol are safely used during pregnancy, the effect of paracetamol overdose on the foetus is unknown. A case of paracetamol overdose was described in a 26-year-old female at 36 weeks gestation. The patient was admitted 4½ hours after ingestion of 22.5 g of paracetamol and promptly placed on the Rocky Mountain Poison and Drug

Center protocol for paracetamol overdose. The patient was successfully treated and delivered a healthy infant girl at 42 weeks gestation. This report indicates that if treatment is begun early and response is rapid, maternal and foetal outcome may be good (if occurring in the third trimester). At this time, it is unknown how much paracetamol is passed to the foetus following a maternal overdose. The capability of the foetus to handle paracetamol is also unknown. If the paracetamol depletes foetal glutathione stores or saturates sulfate conjugation, reactive metabolites would be available to cause foetal liver damage (Byer et al, 1982).

Ibuprofen

Teratogenicity/effects in pregnancy

U.S. Food and Drug Administration's Pregnancy Category B/D (third trimester) (Briggs et al, 1998).

Australian Drug Evaluation Committee's (ADEC) Category C (ADEC, 1996).

Due to known effects on the foetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided.

Breast-feeding: Ibuprofen does not enter human milk in significant quantities (Briggs et al, 1998). The American Academy of Pediatrics considers ibuprofen to be compatible with breast-feeding.

4.7 Effects on Ability to Drive and Use Machines

None.

4.8 Undesirable Effects

Ibuprofen

Cardiovascular system: Tachycardia, flushing, increase in blood pressure.

Central nervous system: Confusion, hallucinations, mental depression, peripheral neuropathy, tinnitus, drowsiness, insomnia.

Gastrointestinal system: Epigastric pain or discomfort, gastritis, haematemesis, gastrointestinal perforation, gastrointestinal ulceration.

Dermatological: Allergic dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Renal: Haematuria, cystitis, renal impairment or failure, polyuria, fluid retention/oedema, acute renal failure, interstitial nephritis, nephrotic syndrome.

Haematological: Agranulocytosis, anaemia, aplastic anaemia, eosinophilia, haemolytic anaemia, leukopenia, thrombocytopenia.

Hypersensitivity reactions: Angiitis, angioedema, bronchospastic allergic reactions, allergic rhinitis, serum sickness-like reaction, systemic lupus erythematosus, aseptic meningitis.

Ophthalmic: Amblyopia, blurred or double vision, conjunctivitis, dry, irritated or swollen eyes, scotoma.

Oral: Aphthous stomatitis, gingival ulcerations.

Ear, nose and throat: Decreased hearing or any change in hearing, epistaxis.

Hepatic effects: Hepatitis.

Pancreatic effects: Pancreatitis.

Paracetamol

Gastrointestinal system: Nausea, vomiting, stomach pain or cramps, diarrhoea, loss of appetite, hepatotoxicity, hepatic failure, hepatic encephalopathy, gastrointestinal tract bleeding, pancreatitis.

Central nervous system: Convulsions, respiratory depression, cerebral oedema, coma.

Haematological: Leucopenia, thrombocytopenia, neutropenia, pancytopenia, agranulocytosis, disseminated intravascular coagulation.

Metabolic: Hypoglycaemia, metabolic acidosis.

Cardiovascular system: Cardiac arrhythmias, cardiovascular collapse.

Renal system: Renal tubular necrosis, renal failure.

Dermatological: Skin rashes and other allergic reactions. The rash is usually erythematous or urticarial but sometimes more serious and may be accompanied by fever and mucosal lesions.

Reporting of suspected adverse reactions

Health care professionals are asked to report any suspected adverse reactions via the https://pv.pharmacyboardkenya.org

4.9 Overdose

Ibuprofen

Symptoms: Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain or, more rarely, diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur if there is a co-incident of dehydration. Exacerbation of asthma is possible in asthmatics.

Management: Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

Paracetamol

Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk factors: If the patient:

- Is on long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Regularly consumes ethanol in excess of recommended amounts.
- Is likely to be glutathione deplete, e.g. cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms: Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management: Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol; however, the maximum protective effect is obtained up to 8 hours post-ingestion.

If required, the patient should be given intravenous N-acetylcysteine in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

Management of patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be discussed with the National Poisons Information Service (NPIS) or a liver unit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

ATC code: N02BE51

<u>Ibuprofen</u>

Ibuprofen most likely produces anti-inflammatory, antipyretic and analgesic effects by inhibition of prostaglandin synthesis. In healthy volunteers, reduction in 6-keto-PGF1a, a stable hydration product of prostacyclin (PGI2) synthesized by renal cortical microsomes, was observed during repeated administration of ibuprofen (400, 800 and 1200 mg daily for 3 days). The decrease was about 50% even with the smallest dose of ibuprofen (Giannessi et al, 1993).

Prevention of colorectal cancer: In vitro, animal, clinical and epidemiological studies lend support for the role of non-steroidal anti-inflammatory drugs (NSAIDs) in preventing colorectal cancer (Shiff & Rigas, 1997; Elder & Paraskeva, 1997). Four mechanisms have been proposed for the chemopreventative effects of NSAIDs: (1) cyclooxygenase (COX)-mediated carcinogen activation, (2) cell proliferation, (3) apoptosis, and (4) immune surveillance. Some mechanisms are believed to occur independently of cyclooxygenase inhibition. COX-1 or COX-2 or both may initiate carcinogenesis by the following mechanisms: (1) direct activation of carcinogens, (2) production of MDA, a mutagen and carcinogen, and (3) production of peroxyl radicals. NSAIDs inhibit the first 2 of the above processes. In addition, colon carcinogens increase COX-1 and COX-2 expression which may increase carcinogen activation. In all tissues, a balance exists between cell renewal and cell loss which is lost in neoplasia. In cell culture, NSAIDs inhibit cell division and alter cell cycle phase distribution of colon cancer cells; it has not been definitively determined whether prostaglandin synthesis is necessary for this effect. Apoptosis, programmed cell death, is inhibited during development of colorectal cancer. NSAIDs induce apoptosis in the colon and rectum. In clinical studies, use of sulindac restored normal apoptosis in the flat rectal mucosa of patients with familial adenomatous polyposis. In cell culture and animal models, colon tumours produce increased quantities of prostaglandin E2 which reduces gene expression of HLA antigens and recognition by immune cells. NSAIDs increase gene expression in colon cancer cells which increases recognition by immune cells. Epidemiological studies provide strong evidence for the prophylactic effect of NSAIDs for preventing colon cancer; however, prospective, controlled studies are needed for confirmation. Additionally, information is needed regarding the age at which chemoprevention should be initiated, the optimal dose and duration of therapy (Shiff & Rigas, 1997; Elder & Paraskeva, 1997).

Paracetamol

Mechanism of action: Paracetamol's mechanism of action appears to be due to inhibition of prostaglandin synthetase centrally. Specifically, it is a potent inhibitor of cyclo-oxygenase in the central nervous system (Amadio, 1984).

5.2 Pharmacokinetic Properties

Ibuprofen

Absorption: It is very well absorbed orally and the peak serum concentration can be attained in 1 to 2 hours after extravascular administration. When ibuprofen is administered immediately after a meal there is a slight reduction in

the absorption rate but there is no change in the extent of the absorption. When orally administered, the absorption of ibuprofen in adults is very rapid in the upper gastrointestinal tract. The average Cmax, Tmax and AUC range around 20 mcg/ml, 2 h and 70 mcg.h/ml. These parameters can vary depending on the enantiomer form, route and dose of administration.

Distribution: The apparent volume of distribution of ibuprofen is 0.1 L/kg.

Protein binding: Ibuprofen is more than 99% bound to plasma proteins and site II of purified albumin; binding appears to be saturable and becomes non-linear at concentrations exceeding 20 mcg/ml.

Metabolism: Ibuprofen is rapidly metabolized and biotransformed in the liver to the formation of major metabolites which are the hydroxylated and carboxylated derivatives. As soon as it is absorbed, the R-enantiomer undergoes extensive enantiomeric conversion (53–65%) to the more active S-enantiomer in vivo by the activity of alpha-methylacyl-CoA racemase. Ibuprofen metabolism can be divided into phase I, which is represented by the hydroxylation of the isobutyl chains for the formation of 2- or 3-hydroxy derivatives followed by oxidation to 2-carboxy-ibuprofen and p-carboxy-2-propionate. These oxidative reactions are performed by the activity of the cytochrome P450 isoforms CYP 2C9, CYP 2C19 and CYP 2C8. Therefore, these enzymes participate in the oxidation of the alkyl side chain to hydroxyl and carboxyl derivatives. Of these enzymes, the major catalyst in the formation of oxidative metabolites is the isoform CYP 2C9. The metabolic phase I is followed by a phase II in which the oxidative metabolites may be conjugated to glucuronide prior to excretion. This activity forms phenolic and acyl glucuronides.

Elimination: Ibuprofen is rapidly metabolized and eliminated in the urine. It is completely eliminated in 24 hours after the last dose and almost all the administered dose goes through metabolism, representing about 99% of the eliminated dose. The biliary excretion of unchanged drug and active phase II metabolites represents 1% of the administered dose.

Paracetamol

Absorption: Rapid and almost complete.

Protein binding: 25%.

Metabolism: Approximately 90 to 95% of a dose is conjugated in the liver with glucuronic acid and sulfuric acid. A small percentage of paracetamol is oxidized by CYP2E1 to form N-acetyl-p-benzo-quinone imine (NAPQI), a toxic metabolite which is then conjugated to glutathione and excreted renally. Accumulation of NAPQI may occur if primary metabolic pathways are saturated.

Route of elimination: Approximately 80% of paracetamol is excreted in the urine after conjugation and about 3% is excreted unchanged.

Half-life: 1 to 4 hours.

5.3 Preclinical Safety Data

Preclinical data reveal no special hazard for humans based on conventional studies of pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Maize starch BP, microcrystalline cellulose BP, colour tartrazine supra IHS, saccharin sodium BP, sodium citrate BP, sodium chloride BP, magnesium stearate BP, capsorama orange DC100 IHS, sodium methyl hydroxybenzoate BP, sodium propyl hydroxybenzoate BP, colloidal anhydrous silica BP and purified water BP.

6.2 Incompatibilities

None.

6.3 Shelf Life

36 months from the date of manufacture.

6.4 Special Precautions for Storage

Store at a temperature not exceeding 30 °C. Protect from light and moisture.

Keep all medicines out of the reach of children.

6.5 Nature and Contents of Container

Blister strip of 10 tablets. 10 strips of 10 tablets each, giving 100 tablets. 60 cartons of 10 strips each, each strip containing 10 tablets, giving 6,000 tablets. 60 cartons are arranged in one layer in a 12 x 5 style. Boxes are then sealed with BOPP tape and a proper identification label is affixed.

6.6 Special Precautions for Disposal and Other Handling

No specific requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

18995/R1

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of renewal: 2026 September 02

10. DATE OF REVISION OF THE TEXT

2026 September 02