NEW ZEALAND DATA SHEET
MAXIGESIC® COLD & FLU HOT DRINK & MAXIGESIC® COLD & FLU HOT DRINK DOUBLE STRENGTH (PARACETAMOL / IBUPROFEN AS LYSINE) POWDER FOR ORAL SOLUTION

1. PRODUCT NAME

Maxigesic® Cold & Flu Hot Drink: paracetamol /ibuprofen (as lysine) powder for oral solution.
Maxigesic® Cold & Flu Hot Drink double strength paracetamol/ibuprofen (as lysine) powder for oral solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Maxigesic® Cold & Flu Hot Drink: each sachet contains paracetamol 500 mg and ibuprofen (as lysine) 150 mg.
Maxigesic® Cold & Flu Hot Drink double strength each sachet contains paracetamol 1000 mg and ibuprofen (as lysine) 300 mg

Excipients with known effect:
Aspartame
Sucrose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral solution.
Light yellow to yellow-coloured powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Maxigesic® Cold & Flu Hot Drink and Maxigesic® Cold & Flu Hot Drink double strength is indicated for the temporary relief of pain associated with: headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, sore throat, arthritis, tennis elbow, period pain, muscular pain, rheumatic pain, aches and pains associated with colds and flu. Reduces fever.

4.2 Dose and method of administration

Dose

Adults and children over 12 years:

Maxigesic® Cold & Flu Hot Drink: the usual dosage is one to two sachets taken every four to six hours, as required, up to a maximum of eight sachets in 24 hours.

Maxigesic® Cold & Flu Hot Drink double strength the usual dosage is one sachet taken every six hours, as required, up to a maximum of four sachets in 24 hours.

Adults should not use Maxigesic® Cold & Flu Hot Drink for more than a few days at a time, unless advised to by a doctor. Children and adolescents aged 12-18 years should not use Maxigesic® Cold & Flu Hot Drink for longer than 48 hours at a time, unless advised to by a doctor.

Dissolved powder should be consumed immediately.

Children under 12 years: Maxigesic® Cold & Flu Hot Drink is not recommended for children under 12 years.

Method of administration

Oral.

Maxigesic® Cold & Flu Hot Drink should be administered by pouring the contents of the sachet into a mug and filling the mug with hot, but not boiling, water. The mixture should be stirred until all powder is dissolved.

4.3 Contraindications

Maxigesic® is contraindicated for use:

- in patients with known hypersensitivity to paracetamol, ibuprofen, aspirin, other NSAIDs or any other ingredients in the product;
- in patients with active alcoholism as chronic excessive alcohol ingestion may predispose patients to paracetamol hepatotoxicity (due to the paracetamol component);
- in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin, ibuprofen or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see section 4.4, Pre-existing asthma).
- in patients with active gastrointestinal bleeding, peptic ulceration or other stomach disorders;
- during the third trimester pregnancy
- in patients with severe heart failure, hepatic failure, or renal failure (glomerular filtration below 30ml/min)
- in patients undergoing treatment of perioperative pain in the setting of coronary artery bypass surgery (CABG).

4.4 Special warnings and precautions for use

Maxigesic® Cold & Flu Hot Drink should not be taken with other products containing ibuprofen, paracetamol, aspirin, salicylates or with any other anti-inflammatory medicines unless under a doctor's instruction. Refer to section 4.5 for additional information.

Gastrointestinal events

Upper gastrointestinal ulcers, gross bleeding or perforation have been described with NSAIDs. The risks increase with dose and duration of treatment, and are more common in patients over the age of 65 years. Some patients will experience dyspepsia, heartburn, nausea, stomach pain or diarrhoea. These risks are minimal when this product is used at the prescribed dose for a few days.

Maxigesic® Cold & Flu Hot Drink should be used with caution, and at the lowest effective dose for the shortest duration, in patients with a history of gastrointestinal haemorrhage or a history of peptic ulcers since their condition may be exacerbated. It is contraindicated in patients with active gastrointestinal bleeding and in those with peptic ulcers or other stomach disorders.
This product should be discontinued if there is any evidence of gastrointestinal bleeding.

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

Cardiovascular thrombotic events

Ibuprofen:

Epidemiological data suggest that use of ibuprofen, particularly at a high dose (2400 mg/daily) may be associated with an increased risk of arterial thrombotic events such as myocardial infarction or stroke. Overall, epidemiological studies do not suggest that low dose ibuprofen (≤ 1200mg/ daily) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating treatment in patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).
There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAIDs use.
Heart failure: Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore, caution is advised in patients with fluid retention or heart failure

Hypertension

Fluid retention, hypertension and oedema have been reported in association with NSAID therapy. NSAIDs may lead to onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensive medicines with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing Maxigesic® to patients with hypertension (see also section 4.3). Blood pressure should be monitored closely during initiation of treatment with Maxigesic® Cold & Flu Hot Drink and at regular intervals thereafter.

Hepatic effects

Patients should be advised to remain alert for hepatotoxicity and be informed about the signs and/or symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, pruritus, jaundice, abdominal tenderness in the right upper quadrant and "flu-like" symptoms). Excessive use can be harmful and increase the risk of liver damage.

Use in Chronic Liver Disease or a History of Liver Disease

Paracetamol:

Paracetamol at higher than recommended doses can lead to hepatotoxicity and even hepatic failure and death. Paracetamol can be used in patients with liver disease and has been studied in both one-time single (1500 mg) and multiple doses (4000 mg/d) in adult patients with chronic stable liver disease. A double-blind, two-period, crossover study was conducted to evaluate the use of 4000 mg/d of paracetamol for 13 days in patients with stable chronic liver disease. There were no abnormalities indicative of an adverse reaction to paracetamol. The metabolism following a single 1500-mg dose was compared in normal subjects, patients with mild liver disease, and patients with severe liver disease. There were no significant differences in overall 24- hour urinary excretion of paracetamol and glucuronide, cysteine, and mercapturic acid conjugates of paracetamol. Following a single (10 mg/kg) dose of paracetamol, the pharmacokinetic profiles in patients with mild, moderate, or severe liver disease were not significantly different. Although the plasma half-life of paracetamol was prolonged in patients with severe liver disease, there were no significant differences in the 24-hour (adult) and 36-hour (children) urinary excretion of paracetamol or its conjugates (glucuronide, cysteine, mercapturic acid).

Ibuprofen:

Patients with impaired liver function or a history of liver disease who are on long term ibuprofen therapy should have hepatic function monitored at regular intervals. Ibuprofen has been reported to have a minor and transient effect on liver enzymes.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis, though rare, have been reported with ibuprofen as with other NSAIDs. If abnormal liver tests persist or worsen, or if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), ibuprofen should be discontinued.

Renal Effects

Caution is also recommended in patients with pre-existing renal disease. Administration of NSAIDs to patients with moderate to severe renal impairment may result in accumulation of paracetamol conjugates. Patients who have been diagnosed with renal impairments must seek medical advice before taking this medication.

Use in Renal Disease

Paracetamol:

Paracetamol can be used in patients with chronic renal disease without dosage adjustment. In a single-dose study, the disposition and metabolite kinetics of 1000 mg of paracetamol were compared in patients

with renal disease and in healthy volunteers. The fractional urinary recovery of paracetamol and its conjugates (e.g., glucuronide, sulphate, cysteine, mercapturate) was similar in healthy volunteers and in patients with moderate renal failure. In a 10-day, multi-dose study, the disposition of paracetamol 3000 mg daily in healthy volunteers was compared with patients with chronic renal failure. A slight increase in predose trough paracetamol levels was noted in patients with renal failure (3.1 μg/mL) compared with controls (1.1 μg/mL), but there was no evidence of accumulation of the glutathione-derived metabolites of paracetamol (e.g., cysteine, mercapturate). Although mean daily predose plasma concentrations of sulphate and glucuronide conjugates were higher in patients with chronic renal disease, these conjugates disappeared rapidly when paracetamol was discontinued. There is no significant risk of paracetamol toxicity in patients with moderate to severe renal failure.

Ibuprofen:

Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration. The two major metabolites of ibuprofen are excreted mainly in the urine and impairment of renal function may result in their accumulation. The significance of this is unknown. NSAIDs have been reported to cause nephrotoxicity in various forms; interstitial nephritis, nephritic syndrome and renal failure. In patients with renal, cardiac or hepatic impairment, those taking diuretics and ACE Inhibitors, and the elderly, caution is required since the use of nonsteroidal anti-inflammatory drugs may result in deterioration of renal function. The dose should be kept as low as possible and renal function should be monitored in these patient.

Renal tubular acidosis and hypokalaemia may occur following treatment with ibuprofen. The risk is increased with higher doses of ibuprofen and following acute overdose, however it may also occur within the recommended dose range.

Presenting signs and symptoms may include reduced level of consciousness and generalised weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and thiazide diuretic at the same time increases the risk of renal impairment (see also section 4.3). This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients.

Severe skin reactions

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), and Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS) (see Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)) which can be fatal and occur without warning. These serious adverse events are idiosyncratic

and are independent of dose or duration of use. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity. Ibuprofen should be discontinued at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

DRESS syndrome has been reported in patients taking NSAIDs. Some of these events have been fatal or life-threatening. DRESS syndrome typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS syndrome may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue the NSAID and evaluate the patient immediately.

Pre-existing asthma

Ibuprofen:

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and NSAIDs has been reported in such aspirin-sensitive patients, ibuprofen tablets should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Ophthalmological effects

Adverse ophthalmological effects have been observed with NSAIDs; accordingly, patients who develop visual disturbances during treatment with products containing ibuprofen should have an ophthalmological examination.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics Ibuprofen: The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Aseptic meningitis

For products containing ibuprofen, aseptic meningitis has been reported only rarely, usually, but not always, in patients with systemic lupus erythematosus (SLE) or other connective tissue disorders.

Masking signs of infection

As with other drugs of this class containing ibuprofen, by reducing fever this may mask the usual signs of infection.

Haematological effects

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency In therapeutic doses, paracetamol does not shorten the lifespan of red blood cells and does not produce any clinically perceptible destruction of circulating red blood cells. It can alter the metabolism of oral anticoagulants (see 4.5 Interaction with other medicines and other forms of interaction).

Blood dyscrasias have been rarely reported. Patients on long-term therapy with ibuprofen should have regular haematological monitoring.

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Coagulation defects

Like other NSAIDs, ibuprofen can inhibit platelet aggregation. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying haemostatic defects, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anti-coagulation therapy.

Special precautions

In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

Use in the elderly

No adjustment in labelled dosage is necessary for older patients who require paracetamol therapy. Those who require therapy for longer than a few days should consult their physician for condition monitoring; however, no reduction in recommended dosage is necessary. However, caution should be taken with regard to the use of ibuprofen as it should not be taken by adults over the age of 65 without consideration of co-morbidities and co-medications because of an increased risk of adverse effects, in particular heart failure, gastrointestinal ulceration and renal impairment (see also section 4.3).

Paediatric use

Maxigesic® Cold & Flu Hot Drink is not recommended for children under 12 years (see also section 4.2).

Effects on laboratory tests

Using current analytical systems, paracetamol does not cause interference with laboratory assays. However, there are certain methods with which the possibility of laboratory interference exists, as described below:

Blood tests:

Paracetamol at recommended doses does not appear to interfere with glucose analysis using currently marketed blood glucose meters. For further detail, it may be advisable to contact the specific laboratory instrumentation manufacturer.

Urine tests:
Paracetamol in therapeutic doses may interfere with the determination of 5-hydroxyindoleacetic acid (5HIAA), causing false-positive results. False determinations may be eliminated by avoiding paracetamol ingestion several hours before and during the collection of the urine specimen.

Female Fertility

The use of ibuprofen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered.

4.5 Interaction with other medicines and other forms of interaction

Anti-platelet agents: Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding

Aminoglycosides: NSAIDs may decrease the excretion of aminoglycosides

Cholestyramine: The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown.

Herbal Extracts: Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

Other analgesics: Avoid concomitant use of two or more NSAIDs, including aspirin and cyclooxygenase-2 (COX-2) selective inhibitors, because of the potential of increased adverse effects.

Ibuprofen antagonizes the irreversible inhibition of platelet cox-1 induced by low dose aspirin. To reduce this effect, ibuprofen should be administered at least 8 hours before or 30 minutes after taking low dose aspirin.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see PHARMACOLOGY).

Cyclosporine or Tacrolimus: Increased risk of nephrotoxicity when used with NSAIDs.

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

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Sulfonylureas: NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of hypoglycaemia in patients on sulfonylurea medications receiving ibuprofen.

CYP2C9 Inhibitors: Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors), an increased S(+)-ibuprofen exposure by approximately 80 to 100% has been shown. Reduction of the ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.

Paracetamol

The following interactions have been noted:

- anticoagulant drugs (e.g. warfarin): dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time;
- antiepileptic medications: the likelihood of toxicity may be increased by the concomitant use of enzyme inducing agents;
- paracetamol absorption is increased by substances that increase gastric emptying, e.g. metoclopramide;
- paracetamol absorption is decreased by substances that decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties, and narcotic analgesics;
- paracetamol may increase chloramphenicol plasma concentrations;
- hepatotoxic drugs or drugs that induce liver microsomal enzymes such as alcohol and anticonvulsant agents: the risk of paracetamol toxicity may be increased in patients receiving these drugs;
- probenecid: may affect paracetamol excretion and plasma concentrations;
- cholestyramine: reduces the absorption of paracetamol if given within 1 hour of paracetamol;
- isoniazid alone or combined with other drugs for tuberculosis: in patients receiving these drugs severe hepatotoxicity at therapeutic doses or moderate overdoses of paracetamol has been reported;
- zidovudine and co-trimoxazole: severe hepatotoxicity has occurred after use of paracetamol in a patients taking these drugs.

Ibuprofen

The following interactions have been noted:

- anticoagulants, including warfarin: ibuprofen interferes with the stability of INR and may increase risk of severe bleeding and sometimes fatal haemorrhage, especially from the gastrointestinal tract. Ibuprofen should only be used in patients taking warfarin if absolutely necessary and they must be closely monitored.
- lithium: ibuprofen may decrease renal clearance and increase plasma concentration of lithium;
- ACE inhibitors, beta-blockers and diuretics: ibuprofen may reduce the anti- hypertensive effect of these drugs and may cause natriuresis and hyperkalaemia in patients under these treatments;

- methotrexate: ibuprofen reduces methotrexate clearance;
- cardiac glycosides: ibuprofen may increase the plasma levels of these drugs;
- corticosteroids: the risk of ibuprofen-induced gastrointestinal bleeding may be increased with concomitant use of oral corticosteroids;
- zidovudine: ibuprofen may prolong bleeding time in patients treated with this drug;
- probenecid, antidiabetic medicine and phenytoin: these medicines may interact with ibuprofen.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C

Maxigesic® Cold & Flu Hot Drink is contraindicated in third trimester of pregnancy.

Maxigesic® Cold & Flu Hot Drink should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus. If there is a compelling need for NSAID treatment during the first or second trimester, limit use to the lowest effective dose and shortest duration possible.

Data from epidemiological studies suggest an increased risk of miscarriage and congenital malformation associated with NSAID use in early pregnancy. Use of NSAIDs in the second or third trimester may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Oligohydramnios is generally seen after days to weeks of treatment, although it has been reported as soon as 48 hours after NSAID initiation. Oligohydramnios is usually, but not always, reversible after treatment discontinuation.

Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue treatment with Maxigesic® Cold & Flu Hot Drink if oligohydramnios occurs. NSAID use during the third trimester may cause premature closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and may delay labour and birth. NSAID use in the third trimester of pregnancy is therefore contraindicated.

Use in lactation

Maxigesic® Cold & Flu Hot Drink is not recommended for nursing mothers.

4.7 Effects on ability to drive and use machines

Following treatment with ibuprofen, the reaction time of patients may be affected. NSAIDS may cause dizziness, drowsiness, fatigue and visual disturbances. If affected patients should not drive or operate machinery.

4.8 Undesirable effects

Paracetamol:

Side effects of paracetamol are rare and usually mild, although haematological reactions have been reports. Skin rashes and hypersensitivity reactions occur occasionally. Overdosage with paracetamol if left untreated can result in severe, sometimes fatal liver damage and rarely, acute renal tubular necrosis.

Ibuprofen:

Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of non-specific allergic reaction and anaphylaxis, respiratory tract reactivity compromising asthma, aggravated asthma, bronchospasm, or dyspnoea, or assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and very rarely, bullous dermatoses (including Steven-Johnson Syndrome, toxic epidermal necrolysis and erythema multiforme).

More common reactions: (greater than 1%)

Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature. Gastrointestinal complaints include nausea, epigastric pain, heartburn diarrhoea, abdominal distress, nausea and vomiting, dyspepsia, constipation, abdominal cramps or pain, gastrointestinal haemorrhage, haematemesis, melaena, fullness of the GI tract (bloating and flatulence).

Ear and Labyrinth disorders: Tinnitus, hearing impaired.

General disorders and administration site conditions. Oedema, fluid retention; fluid retention generally responds promptly to discontinuation of the drug.

Nervous system disorders: Dizziness, headache, nervousness

Skin and subcutaneous tissue disorders: Rash (including maculopapular type), pruritus.

General disorders: Decreased appetite, fatigue.

Less common reactions (less than 1%)

Nervous system disorders: Depression, insomnia, anxiety, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma.

Skin and subcutaneous tissue disorders: Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, mouth ulceration, ulcerative stomatitis, pancreatitis, gastritis. Exacerbation of colitis and Crohn's Disease (see Contraindications section).

Hepatobiliary disorders: Hepatitis, Jaundice, abnormal liver function

Blood and lymphatic system disorders: Neutropenia, leucopoenia, agranulocytosis, aplastic anaemia, (sometimes Cooms positive), thrombocytopenia with or without purpura, eosinophilia and decrease in haemoglobin and haematocrit.

Cardiac disorders: Cardiac failure, myocardial infarction

Vascular disorder: Hypertension

Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm, dyspnoea

Infections and infestations: Rhinitis and meningitis aseptic

Eye disorders: Amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision) have occurred but is usually reversed after cessation of therapy. Any patient with eye complaints should have an ophthalmological examination which includes central vision fields. Visual impairment and toxic neuropathy have also been reported.

Allergic: Syndrome of abdominal pain, fever, chills, nausea and vomiting, anaphylaxis.

Precise Incidence Unknown (but less than 1%) Causal Relationship Unknown

Nervous System disorders: Paraesthesia's, hallucinations, dream abnormalities, vertigo

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, photoallergic skin reactions
Unknown: Drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP),. Photosensitivity reactions.

Eye disorders: Conjunctivitis, diplopia, optic neuritis, cataracts

Blood and lymphatic system disorders: Bleeding episodes (e.g. epistaxis, menorrhagia)

Metabolism and nutrition disorders: Gynaecomastia, hypoglycaemic reaction, acidosis

Renal and urinary disorders: Renal nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

Hepatobiliary disorders: Abnormal liver function, hepatic failure, hepatitis and jaundice.

Cardiac disorders: Arrythmias (sinus tachycardia, sinus bradycardia)

Immune system disorders: Serum sickness, lupus erythematosus syndrome, Henoch-Scholein vasculitis, angioedema

Post-marketing experience

Oligohydramnios, neonatal renal impairment

Renal tubular acidosis* (Frequency is 'Not known').
Hypokalaemia* (Frequency is 'Not known').
*The risk is increased with higher doses of ibuprofen and following acute overdose, however it may also occur within the recommended dose range.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at: https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage. Symptoms

Paracetamol

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 proceed to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop in the absence of severe liver damage. Cardiac arrhythmias have been reported. Liver damage is likely in adults who have taken 10 g or more of paracetamol, due to excess quantities of a toxic metabolite becoming irreversibly bound to liver tissue.

Ibuprofen

Symptoms include nausea, abdominal pain and vomiting, dizziness, convulsion and rarely, loss of consciousness. Clinical features of overdose with ibuprofen which may result are depression of the central nervous system and the respiratory system.

Renal tubular acidosis and hypokalaemia may occur. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8)

Treatment

Paracetamol:

Prompt treatment is essential in the management of paracetamol overdosage even when there are no obvious symptoms, and should not be delayed while waiting for laboratory results. Specific therapy with an antidote such as acetylcysteine (intravenous) or methionine (oral) should be instituted as soon as possible.

Acetylcysteine is most effective when administered during the first 8 hours following ingestion of the overdose and the effect diminishes progressively between 8 and 16 hours. It used to be believed that starting treatment more than 15 hours after overdosage was of no benefit and might possibly aggravate the risk of hepatic encephalopathy. However, late administration has now been shown to be safe, and studies of patients treated up to 36 hours after ingestion suggest that beneficial results may be obtained beyond 15 hours. Furthermore, administration of intravenous acetylcysteine to patients who have already

developed fulminant hepatic failure has been shown to reduce morbidity and mortality.

An initial dose of 150 mg/kg of acetylcysteine in 200 mL 5% glucose is given intravenously over 15 minutes, followed by an I.V. infusion of 50 mg/kg in 500 mL 5% glucose over 4 hours and then 100 mg/kg in 1 litre 5% glucose over 16 hours. The volume of I.V. fluids should be modified for children.

Methionine is given orally as 2.5 g every 4 hours up to 10 g. Methionine treatment must be started within 10 hours after ingestion of paracetamol; otherwise it will be ineffective and may exacerbate liver damage.

Evidence of serious symptoms may not become apparent until 4 or 5 days following overdosage and patients should be carefully observed for an extended period.

Ibuprofen:

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount of ibuprofen, use of activated charcoal should be considered.

For information on the management of overdose, contact the Poisons Information Centre on 0800 764 766 (New Zealand)

5. PHARMACOLOGICAL PROPERTIES

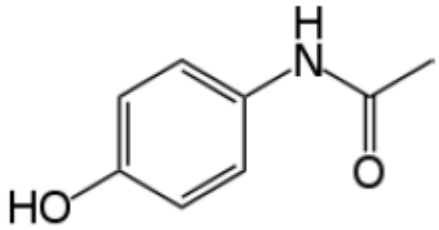
5.1 Pharmacodynamic properties

Paracetamol:

Chemical Name: N-acetyl-p-aminophenol

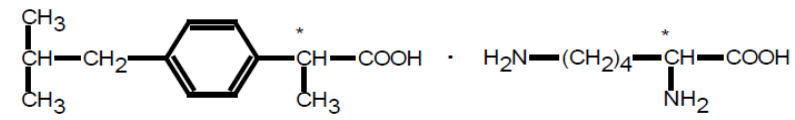
CAS number: 103-90-2 Structural

Formula:



Ibuprofen:

The chemical name for ibuprofen (as lysine) is: (±)-2-(p-isobutylphenyl) propionic acid, (±) Lysine salt. It has the following structural formula:



CAS number: 57469-76-8

Mechanism of action

Paracetamol

Although the exact site and mechanism of analgesic action is not clearly defined, paracetamol appears to produce analgesia by elevation of the pain threshold. The potential mechanism may involve inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and substance P.

Ibuprofen

Ibuprofen possesses analgesic, antipyretic and anti-inflammatory properties, similar to other non-steroidal anti-inflammatory drugs (NSAIDs). Its mechanism of action is unknown, but is thought to be through peripheral inhibition of cyclooxygenases and subsequent prostaglandin synthesise inhibition.

Clinical trials

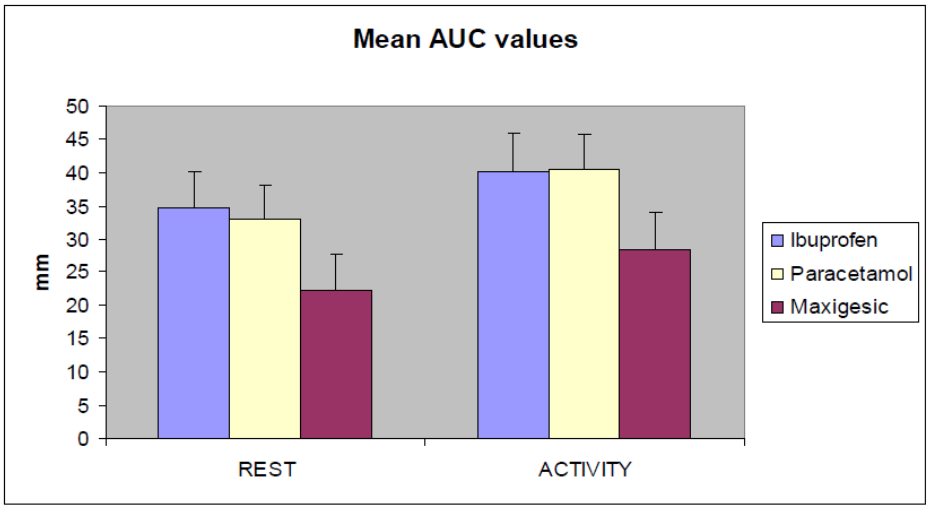
Maxigesic® Cold & Flu Hot Drink is an alternative dosage form of the product Maxigesic® tablets. One sachet of Maxigesic® Cold & Flu Hot Drink (paracetamol 500 mg/ibuprofen 150 mg) is equivalent to one Maxigesic® tablet. One sachet of Maxigesic® Cold & Flu Hot Drink Double Strength (paracetamol 1000 mg/ibuprofen 300 mg) is equivalent to two Maxigesic® tablets.

A prospective, parallel group, double-blind comparison of the analgesic effect of Maxigesic® tablets, paracetamol alone, or ibuprofen alone in 135 patients with post-operative dental pain for 48 hours following oral surgery was conducted. The oral surgery was conducted under local or general anaesthetic with one dose of oral analgesic (2 tablets of paracetamol 500 mg or ibuprofen 300 mg or Maxigesic®) given pre-operatively. Total dose in the 24 hours were paracetamol 4000 mg, ibuprofen 1200 mg and Maxigesic®. Analgesia, the primary efficacy end point, was a time-corrected AUC (Area Under the Curve) calculated from 100 mm VAS (Visual Analogue Scale) pain scores over 48 hours at both rest and on activity.

The primary end points, assessed on the Intent to Treat (ITT) population, showed the mean time-adjusted AUCs over 48 hours calculated from the VAS pain scores for Maxigesic® were significantly lower than for paracetamol at rest (22.344 [SE 3.2] and 33.016 [3.005], respectively [p=0.007]), and on activity (28.377 [SE 3.396] and 40.364 [SE 3.271], respectively [p=0.006]).

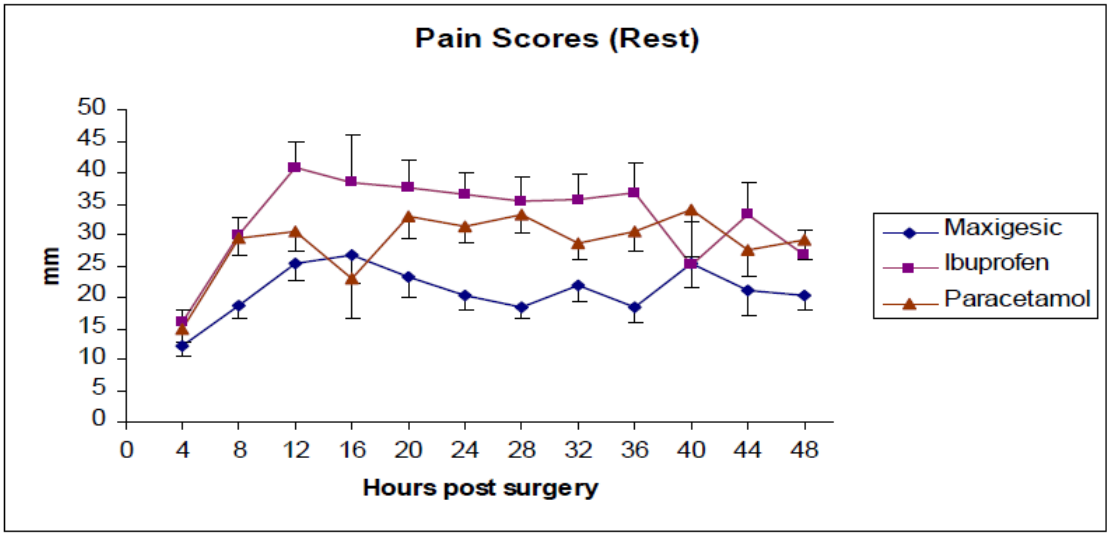
A similar outcome is seen for the Maxigesic® comparison where the AUCs over 48 hours showed the VAS for the combination drug were significantly lower than for ibuprofen at rest (22.344 [SE 3.2] and 34.78 [SE 3.22], respectively [p=0.003]), and during activity (28.377 [SE 3.396] and 40.217 [SE 3.418], respectively [p=0.007]).

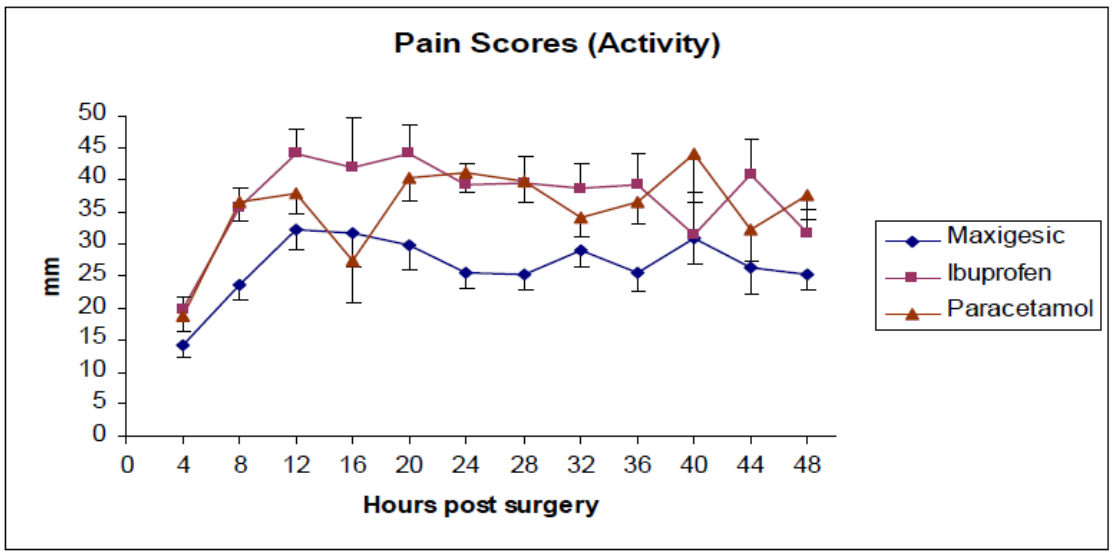
Figure 1: Means of time-adjusted AUC at rest and on activity by treatment groups.



A presentation of the pain records during the 48 hours also shows the Maxigesic® analgesic effect showed lower mean pain scores than either of its two active ingredients at almost all time points at both rest and during activity (Figure 2).

Figure 2: Pain score plot – scores given are those rated during each 4-hour period post-surgery.





A double-blind, placebo-controlled, randomised, parallel group comparison trial was conducted in 159 participants experiencing pain from removal of 2-4 molars. Three different possible doses of Maxigesic® were evaluated and compared with that of placebo [N=49]. The doses corresponded to half [N=46], one [N=34] or two tablets [N=30] of Maxigesic® given four times a day for 24 hours.
The mean-adjusted Sum of Pain Intensity Difference [SPID] in all the Maxigesic® doses were significantly [p=0.004-0.002] higher than placebo consistent with each possible dose of Maxigesic® being more effective than placebo.

The results demonstrating the SPID, response rate, maximum VAS pain scores and percentage of patients requiring rescue medication for all four study groups (placebo, half, one and two tablet doses) are presented in the table below.

	Maxigesic® (two tablets: 1000mg paracetamol + 300 mg ibuprofen) N=30	Maxigesic® (one tablet: 500mg paracetamol + 150 mg ibuprofen) N=34	Maxigesic® (half tablet: 250 mg paracetamol + 75 mg ibuprofen) N=46	Placebo N=49
		SPIDs (mm)		
Mean (SD)	**20.12(18.01)**	**20.44(20.78)**	**19.25(19.99)**	**6.63(19.79)**
P value	0.004	0.002	0.002	-
		Response Rate* (%)		
Yes (%)	50.00%	44.10%	45.70%	18.4%
P value	**0.003**	**0.011**	**0.008**	-
		Maximum VAS Pain Scores (mm)		
Mean (SD)	**51.13(13.22)**	**55.38(17.61)**	**54.98(15.92)**	**61.20(18.34)**
P value	0.009	**0.063**	**0.062**	-
		Percentage of Participants Requiring Rescue Medication (%)		
Yes (%)	53.30%	61.80%	56.50%	81.60%
P value	**0.007**	**0.044**	**0.008**	-

**Response rate = percentage of patients with a decrease of at least 50% in VAS pain score within 6 hours after the first dose.*

5.2 Pharmacokinetic properties

Absorption

Paracetamol is absorbed from the gastrointestinal tract with peak plasma concentration occurring about 10 to 60 minutes after oral administration.

Ibuprofen is absorbed following oral administration with maximum plasma concentrations usually achieved in 60 to 120 minutes.

Distribution

Paracetamol is distributed into most body tissues. Ibuprofen is highly protein bound.

Metabolism

Paracetamol is metabolised extensively in the liver and excreted in the urine, mainly as inactive glucuronide and sulphate conjugates. Less than 5% is excreted unchanged. The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This active intermediate is detoxified by conjugation with glutathione, however, it can accumulate following paracetamol overdosage and if left untreated has the potential to cause severe and even irreversible liver damage.

Paracetamol is metabolised differently by premature infants, newborns, and young children compared with adults, the sulphate conjugate being most predominant.

Ibuprofen is highly bound (90-99%) to plasma proteins and is extensively metabolised to inactive compounds in the liver, mainly by glucuronidation.

The metabolic pathways of paracetamol and ibuprofen are distinct and there should be no drug interactions where the metabolism of one affects the metabolism of the other. A formal study using human liver enzymes to investigate such a possibility failed to find any potential drug interaction on the metabolic pathways.

In another study, the effect of ibuprofen on the oxidative metabolism of paracetamol was evaluated in healthy volunteers under fasting conditions. The study results indicated that ibuprofen did not alter the amount of paracetamol undergoing oxidative metabolism, as the amount of paracetamol and its metabolites (glutathione-, mercapturate-, cysteine-, glucuronide- and sulfate-paracetamol) were similar when administered alone, as paracetamol, or with the concomitant administration of ibuprofen (as a fixed combination Maxigesic®).

Excretion

Paracetamol elimination half-life varies from about 1 to 3 hours.

Both the inactive metabolites and a small amount of unchanged ibuprofen are excreted rapidly and completely by the kidney, with 95% of the administered dose eliminated in the urine within four hours of ingestion. The elimination half-life of ibuprofen is in the range of 1.9 to 2.2 hours.

Pharmacokinetic/pharmacodynamic relationship(s)

A specific study to investigate possible effects of paracetamol on the plasma clearance of ibuprofen and vice versa did not identify any drug interactions.

5.3 Preclinical safety data

Potential Laboratory Test Interferences

Paracetamol:

Using current analytical systems, paracetamol does not cause interference with laboratory assays.

However, there are certain methods with which the possibility of laboratory interference exists, as described below:

Blood Tests

Paracetamol at recommended doses does not appear to interfere with glucose analysis using currently marketed blood glucose meters. For further detail, it may be advisable to contact the specific laboratory instrumentation manufacturer.

Urine Tests

Paracetamol in therapeutic doses may interfere with the determination of 5hydroxyindoleacetic acid (5HIAA), causing false-positive results. False determinations may be eliminated by avoiding paracetamol ingestion several hours before and during the collection of the urine specimen.

Carcinogenicity/Mutagenicity

Paracetamol:

Various animal bioassays on a weight-of-evidence basis have demonstrated no evidence of carcinogenic potential for paracetamol.

Carcinogenicity (Human)

Although it has been hypothesized that long-term use of analgesics may be associated with a slight increase in urinary tract tumours and renal cell cancer in man, a number of population- based, case-controlled studies have shown that it is unlikely that paracetamol use plays a major role in renal cell cancer.

A comprehensive and conclusive review, accepted by the Committee for Proprietary Medicinal Products (CPMP) of the European Union, considered the genotoxic and carcinogenic properties of paracetamol. This review concluded that genotoxic effects of paracetamol are not reached at therapeutic dosage.

Reproductive and Teratogenic Effects (Animal)

There was no effect on pregnancy or offspring when paracetamol was given at dose levels of 600 mg/kg/d in the diet of male rats for 60 days prior to mating and to female rats from 14 days before mating to the end of pregnancy. An oral dose of 600 mg/kg/d produced no teratogenicity or embryotoxicity when given from days 6 through 15 of pregnancy. When paracetamol was given from day 16 of pregnancy through a

3-week lactation period, no deleterious effect was noted on pregnancy rate or on percent of live births, but a decrease in body weight gain and survival rate was noted among offspring of drug-treated females. In another study, paracetamol 250 mg/kg/d did not affect foetal length or weight, incidence of resorptions, or placental weight.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame
Curcumin 95%
Lemon flavour
Sodium citrate dihydrate
Sucrose

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

36 months for product manufactured by Rubicon.

30 months for product manufactured by EPharma.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Maxigesic® Cold & Flu Hot Drink is supplied in 4-ply laminate sachets, in cartons containing 10, 16, 20, 24 or 30 sachets. Not all pack sizes may be marketed.

Maxigesic® Cold & Flu Hot Drink double strength is supplied in 4-ply laminate sachets, in cartons containing 10, 12 sachets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Maxigesic® Cold & Flu Hot Drink
Pack size of 10, 16 or 20 sachets: General Sale Medicine
Pack sizes of 24 or 30 sachets: Pharmacy Only

Maxigesic® Cold & Flu Hot Drink Double Strength
Pack sizes of 10 or 12 sachets: Pharmacist Only

8. SPONSOR

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9. DATE OF FIRST APPROVAL

30.06.2022

10. DATE OF REVISION

10.05.2024

11. SUMMARY TABLE OF CHANGES

Section changed	Summary of New Changes
4.4 Special warnings and precautions for use 4.8 Undesirable effects 4.9 Overdose	Included warnings for risks of renal tubular acidosis and hypokalaemia