MAXIGESIC® IV
PARACETAMOL / IBUPROFEN (AS SODIUM DIHYDRATE) SOLUTION FOR INFUSION

1. NAME OF THE MEDICINE

Paracetamol 1000 mg/ibuprofen (as sodium dihydrate) 300 mg in 100 mL solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mL vial contains paracetamol 1000 mg and ibuprofen (as sodium dihydrate) 300 mg. Excipients

with known effect:
Sodium 35.06 mg per 100 mL (0.35 mg/mL). For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Maxigesic® IV is indicated in adults for the relief of post-operative pain, where an intravenous route of administration is considered clinically necessary.

4.2 Dose and method of administration

Dose
Administer one vial (100 mL) Maxigesic® IV as a 15-minute infusion every 6 hours, as necessary. Do not exceed a total daily dose of 4000 mg (4 g) paracetamol.

In patients with hepatotoxic risk, the maximum daily dose is 3000 mg (3g) paracetamol (see Hepatic impairment below).

Special populations
Paediatric population
The safety and efficacy of Maxigesic® IV in children aged under 18 years have not been established. Maxigesic® IV is contraindicated in patients under the age of 18 years.

Elderly
Clinical studies of Maxigesic® IV did not include sufficient numbers of subjects 65 years of age and

over to determine whether they respond differently to younger subjects. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients are at increased risk for serious GI adverse events (see section 4.4, Gastrointestinal effects).

Renal impairment
Caution should be taken with ibuprofen dosage in patients with renal impairment. This medicinal product is contraindicated in patients with severe renal failure.

The dosage should be assessed individually. The initial dose should be reduced in patients with mild to moderate renal impairment. The dose should be kept as low as possible and be used for the shortest possible duration necessary to control the symptoms. Renal function should be monitored.

Hepatic impairment
The use of paracetamol at higher than recommended doses can lead to hepatotoxicity and even hepatic failure and death. In patients with additional risk factors for hepatotoxicity, like hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of glutathione in the liver), or dehydration, a total daily dose of 3000 mg (3 g) paracetamol should not be exceeded.

This medicinal product is contraindicated in patients with severe hepatic failure. A patient with symptoms and/or signs suggesting liver dysfunction, or with abnormal liver test values, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with ibuprofen and Maxigesic® IV should be discontinued. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), Maxigesic® IV should be discontinued.

Adverse gastrointestinal events
To minimise the potential risk for an adverse GI event in patients treated with a NSAID, use the lowest effective dose for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI event is suspected.

This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Method of administration
Maxigesic® IV should be administered as a 15-minute intravenous infusion.

Visually inspect Maxigesic® IV for particulate matter and discolouration prior to administration, whenever solution and container permit. If visibly opaque particles, discolouration or other foreign particulates are observed, the solution should not be used.

Maxigesic® IV should be used in one patient on one occasion only. It contains no antimicrobial preservative. Unused solution should be discarded.

As for all solutions for infusion presented in glass vials, it should be remembered that close monitoring is needed notably at the end of the infusion, regardless of administration route. This monitoring at the

end of the perfusion applies particularly for central route infusion, in order to avoid air embolism.

It is recommended that for the administration of Maxigesic® IV a syringe or giving set with a diameter equal to or below 0.8 mm should be used for solution sampling. In addition, it is recommended that the bung is pierced at the location specifically designed for needle introduction (where the thickness of the bung is the lowest). If these recommendations are not adhered to the likelihood of bung fragmentation or the bung being forced into the vial is increased.

To facilitate administration, the label attached to the vials of Maxigesic® IV allow for hanging.

4.3 Contraindications

Maxigesic® IV is contraindicated:

- in patients with hypersensitivity to the active substances or to any of the excipients listed in section 6.1;
- in patients with active alcoholism, as chronic excessive alcohol ingestion may predispose patients to paracetamol hepatoxicity (due to the paracetamol component);
- in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal anaphylactic-like reactions to NSAIDs have been reported in such patients (see section 4.4);
- for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see section 4.4);
- in patients with severe hepatic failure or severe renal failure
- in patients with severe heart failure (NYHA Class IV);
- in patients with cerebrovascular or other active bleeding;
- in patients with dengue hemorrhagic fever
- in patients with active gastrointestinal bleeding, peptic ulceration or other stomach disorders;
- in patients with spinal cord injuries;
- during pregnancy or in patients planning to become pregnant;
- during breastfeeding.
- in patients under the age of 18 years

It is recommended to use a suitable analgesic oral treatment as soon as this administration route is possible.

In order to avoid the risk of overdose, check that other medicines administered do not contain paracetamol.

Doses higher than the recommended entail a risk of very serious liver damage. Clinical symptoms and signs of liver damage are usually seen first after two days with a maximum usually after 4 to 6 days. Treatment with antidote should be given as soon as possible (see section 4.2).

4.4 Special warnings and precautions for use

Maxigesic® IV should be used with caution in cases of:

- Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency (may lead to haemolytic anaemia),
- anorexia, bulimia or cachexia; chronic malnutrition (low reserves of hepatic glutathione), dehydration,

hypovolemia. (See sections 4.2 and 5.2).

Maximum daily dose

The total dose of paracetamol should not exceed 4 g per day. In patients with additional risk factors for hepatotoxicity, like hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of glutathione in the liver), or dehydration, a maximum daily dose of 3000 mg (3 g) paracetamol should not be exceeded. It is important to consider the contribution of all paracetamol-containing medications, including non-prescription, oral or PR forms of the drug to this total daily paracetamol dose prior to administering Maxigesic® IV. If the daily dose of paracetamol from all sources exceeds the maximum, severe hepatic injury may occur (see section 4.9).

Duration of dosage

Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. Maxigesic® IV should be administered as a 15-minute intravenous infusion of 1000 mg paracetamol and 300 mg ibuprofen (as sodium dihydrate) in 100 mL, every 6 hours as necessary. Do not exceed a total daily dose of 4000 mg (4 g) paracetamol. Use of the recommended maximum dose of Maxigesic® IV of 100 mL every 6 hours has only been studied for a period of up to 2 days.

Hepatic injury

Acetaminophen

Maxigesic® IV contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 mg per day, and often involve more than one acetaminophen-containing product.

The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.

Ibuprofen

Maxigesic® IV contains ibuprofen, a NSAID. Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs, including ibuprofen.

Clinical Recommendations Maxigesic® IV is contraindicated in patients with severe hepatic impairment or severe active liver disease. Maxigesic® IV has not been studied in patients with impaired hepatic function. Use in these patients is not recommended.

If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue Maxigesic® IV immediately, and perform a clinical evaluation

of the patient.

Cardiovascular thrombotic events

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. 1200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Hypertension

NSAIDs, including the ibuprofen in Maxigesic® IV, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Use NSAIDs, including Maxigesic® IV, with caution in patients with hypertension.

Monitor blood pressure closely during the initiation of NSAID treatment and throughout the course of therapy. Patients taking ACE inhibitors, thiazides, or loop diuretics may have an impaired response to these therapies when taking NSAIDs.

Congestive heart failure and oedema

Fluid retention and oedema have been observed in some patients taking NSAIDs. Use Maxigesic® IV with caution in patients with fluid retention or heart failure.

Gastrointestinal effects: risk of ulceration, bleeding, and perforation

Serious GI toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Minor upper GI problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Studies have shown that patients with a prior history of peptic ulcer disease and/or GI bleeding and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have

identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Most reports of spontaneous fatal GI events are in elderly or debilitated patients, and therefore special care should be taken in treating this population.

To minimise the potential risk for an adverse GI event in patients treated with a NSAID, use the lowest effective dose for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Serious skin reactions

NSAIDs, including the ibuprofen in Maxigesic® IV, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin manifestations, and discontinue Maxigesic® IV at the first appearance of skin rash or any other sign of hypersensitivity (see also section 4.3).

Pre-existing asthma

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 between aspirin and NSAIDs has been reported in such aspirin-sensitive patients, including bronchospasm, Maxigesic® IV is contraindicated in patients with this form of aspirin sensitivity and should be used with caution in all patients with pre-existing asthma (see also section 4.3).

Ophthalmological effects

Blurred or diminished vision, scotomata, and changes in colour vision have been reported with oral ibuprofen. Discontinue ibuprofen if a patient develops such complaints, and refer the patient for an ophthalmologic examination that includes central visual fields and colour vision testing.

Hepatic effects

Borderline elevations of one or more liver tests may occur in some patients taking NSAIDs, including the ibuprofen in Maxigesic® IV. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in small numbers of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions have been reported, including jaundice, fulminant hepatitis, liver necrosis and hepatic failure, some with fatal outcomes. A patient with symptoms and/or signs suggesting liver dysfunction, or with abnormal liver test values, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with ibuprofen. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Maxigesic® IV should be discontinued.

Renal effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in renal prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE inhibitors, or angiotensin receptor antagonists, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

Caution is also recommended in patients with pre-existing renal disease. No information is available from controlled clinical studies regarding the use of Maxigesic® IV in patients with advanced renal disease. If Maxigesic® IV therapy must be initiated in patients with advanced renal disease, closely monitor the patient's renal function.

Aseptic meningitis

Aseptic meningitis with fever and coma has been observed in patients on oral ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on Maxigesic® IV, give consideration to whether or not the signs or symptoms are related to ibuprofen therapy.

Haematological effects

Anaemia may occur in patients receiving NSAIDs, including the ibuprofen in Maxigesic® IV. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect on erythropoiesis. In patients on long-term treatment with NSAIDs, including ibuprofen, check haemoglobin or haematocrit if they exhibit any signs or symptoms of anaemia or blood loss.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effects on platelet function are less severe quantitatively, of shorter duration, and reversible. Carefully monitor patients who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients with dengue hemorrhagic fever or patients receiving anticoagulants.

Masking inflammation and fever

The pharmacological activity of ibuprofen in Maxigesic® IV in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed non-infectious, painful conditions.

Anaphylactoid reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to ibuprofen. Maxigesic® IV is contraindicated in patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see also section 4.3).

Patients receiving spinal or epidural analgesia
As potential bleeding around the spinal cord has serious consequences, caution should be exercised when treating patients undergoing spinal and epidural analgesia.

Monitoring
Serious GI tract ulcerations and bleeding can occur without warning symptoms, therefore physicians should monitor for signs or symptoms of GI bleeding.

Patients on long-term treatment with NSAIDs should have full blood count (FBC) and chemistry profiles checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash), or abnormal liver tests persist or worsen, discontinue Maxigesic® IV.

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 products containing ibuprofen are added to the treatment program.

In-house compounded solutions
Maxigesic® IV has been specifically formulated to provide a stable solution of paracetamol and ibuprofen. Commercially available formulations of each active ingredient alone should not be mixed together in order to produce a substitute for Maxigesic® IV, as precipitation may occur.

Use in the elderly
Decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy, are more common in the elderly population. In addition, elderly patients are at increased risk of serious GI adverse events. Dose selection in elderly patients should be cautious (see sections 4.2 and 4.4, Gastrointestinal effects).

Paediatric use
Maxigesic® IV is indicated for use in adults only; safety and efficacy in children aged under 18 years have not been established (see 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.

4.5 Interactions with other medicines and other forms of interaction

Aminoglycosides
NSAIDs may decrease the excretion of aminoglycosides.

Anticoagulants
The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that the users of both drugs together have a higher risk of serious GI bleeding than users of either drug alone (see section 4.4).

Antidiabetic medicines
These medicines may interact with ibuprofen.

Aspirin
When ibuprofen is administered with aspirin, ibuprofen's protein binding is reduced, although the clearance of free ibuprofen is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of Maxigesic® IV and aspirin is not generally recommended because of the potential for increased adverse effects.

Busulfan
Busulfan is eliminated from the body via conjugation with glutathione. Concomitant use with paracetamol may result in reduced busulfan clearance.

Cardiac glycosides
NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma cardiac glycoside levels. Care should therefore be taken in patients treated with cardiac glycosides.

Chloramphenicol
Paracetamol may increase chloramphenicol plasma concentrations.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics
NSAIDs may diminish the antihypertensive effect of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors. Ibuprofen, like other NSAIDs, can reduce the antihypertensive effect of ACE inhibitors and beta-blockers with possible loss of blood pressure control and can attenuate the natriuretic effects of thiazide diuretics and frusemide. Diuretics can also increase the risk of nephrotoxicity of NSAIDs. The combined use of the three classes of drugs, thiazides, an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist) and an anti-inflammatory drug (NSAID or COX-2 inhibitor) all at the same time increases the risk of renal impairment (see section 4.4, Renal effects).

Corticosteroids
Increased risk of gastrointestinal bleeding.

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

Diflunisal
Concomitant diflunisal increases paracetamol plasma concentrations and this may increase hepatotoxicity.

Diuretics
Clinical studies and postmarketing observations have shown that ibuprofen can reduce the natriuretic effects of frusemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, observe patients closely for signs of renal failure, as well as to assure diuretic efficacy (see section 4.4).

Enzyme-inducing agents
Caution should be paid to the concomitant intake of enzyme-inducing agents. These substances include but are not limited to: barbiturates, isoniazid, anticoagulants, zidovudine, amoxicillin + clavulanic acid, carbamazepine and ethanol. Induction of metabolism of paracetamol from enzyme inducers may result in an increased level of hepatotoxic metabolites.

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

Lithium
Maxigesic® IV should be avoided in patients taking lithium as NSAIDs have produced elevations of plasma lithium levels and a reduction in renal lithium clearance.

Methotrexate
NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This indicates that NSAIDs may enhance the toxicity of methotrexate. Use caution when NSAIDs are administered concomitantly with methotrexate.

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

Phenytoin
Phenytoin administered concomitantly may result in decreased paracetamol effectiveness and an increased risk of hepatotoxicity. Patients receiving phenytoin therapy should avoid large and/or chronic doses of paracetamol. Patients should be monitored for evidence of hepatotoxicity. Phenytoin may also interact with ibuprofen.

Probenecid
Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation

with glucuronic acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid. Probenecid may also interact with ibuprofen.

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.

Zidovudine
Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Monitoring
Serious GI tract ulcerations and bleeding can occur without warning symptoms, therefore physicians should monitor for signs or symptoms of GI bleeding.

Patients on long-term treatment with NSAIDs should have FBC and chemistry profiles checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g. eosinophilia, rash), or abnormal liver tests persist or worsen, discontinue Maxigesic® IV.

4.6 Fertility, pregnancy and lactation

Effects on fertility
The effects of Maxigesic® IV on fertility are unknown.

Intravenous paracetamol (administered as propacetamol) had no effect on fertility of rats at systemic exposure levels (based on AUC) greater than twice those anticipated at the maximum clinical dose.

In rats, fertility was not affected by dietary administration of ibuprofen 20 mg/kg/day to males and females from prior to mating through organogenesis, or by oral administration to females at up to 180 mg/kg/day throughout gestation. In rabbits, oral administration of ibuprofen 60 mg/kg/day throughout gestation was associated with reduced implantations and live litter size, along with maternotoxicity; the no-effect dose was 20 mg/kg/day (see also section 4.6, Pregnancy).

Use in pregnancy Category C

There are no adequate, well-controlled studies in pregnant women. As there is insufficient information on the use of Maxigesic® IV during pregnancy, its use during pregnancy or in patients planning to become pregnant is contraindicated (see also section 4.3, Contraindications).

Data from epidemiological studies suggest an increased risk of miscarriage after the use of a prostaglandin synthesis inhibitor in early pregnancy. Prior to week 30 of pregnancy, Maxigesic® IV

should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. From week 30 of pregnancy, Maxigesic® IV and other NSAIDs can cause foetal harm and should be avoided by pregnant women. NSAIDs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the foetal ductus arteriosus, foetal renal impairment, inhibition of platelet aggregation, and delay labour and birth. Continuous treatment with NSAIDs during the third trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, NSAIDs should be avoided.

There was no evidence of developmental abnormalities following oral administration of ibuprofen to rats and rabbits throughout gestation at respective doses up to 180 and 60 mg/kg/day.

Paracetamol has been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

The reproductive toxicity of IV paracetamol has not been directly tested in animal studies. IV administration of maternotoxic doses of the pro-drug, propacetamol, to pregnant rats and rabbits during organogenesis increased the incidence of extranumerary ribs and sacral vertebrae (normal variations in these species) at 0.7-fold (rabbits; mg/m^2 basis) and 7-fold (rats; AUC basis) the maximum anticipated clinical exposure to paracetamol. The clinical significance of these findings is not known. No signs of pre/post-natal toxicity were observed in rats treated with IV propacetamol at maternal exposures (based on AUC) greater than 3-fold those anticipated at the maximum clinical dose.

Labour and delivery
The effects of Maxigesic® IV on labour and delivery in pregnant women are unknown but, based on the known pharmacology of ibuprofen, administration is not recommended as the onset of labour may be delayed and the duration increased with a greater bleeding tendency in both mother and child (see also section 4.6, Pregnancy).

Use in lactation
After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported.

No signs of toxicity were observed in rat pups of dams that received IV propacetamol postpartum at maternal exposures (based on AUC) greater than twice those anticipated at the maximum clinical dose.

It is not known whether ibuprofen and/or its metabolites are excreted in human milk. Because many drugs are excreted in milk and because of the potential for serious adverse reactions in nursing infants from IV ibuprofen, Maxigesic® IV is contraindicated for use in nursing mothers (see also section 4.3, Contraindications).

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for drowsiness, dizziness, light-headedness, or blurred vision and advised not to drive or operate machinery if these symptoms occur or until their individual

susceptibility is known.

4.8 Adverse effects (Undesirable effects)

a. Summary of the safety profile

Clinical trials with Maxigesic® IV have not indicated any undesirable effects other than those for paracetamol alone or ibuprofen alone.

In a phase III study in 276 patients undergoing bunionectomy surgery, the most common treatment emergent adverse events (TEAEs) were gastrointestinal disorders (38.8%), followed by nervous system disorders (28.6%). The incidence of TEAEs was comparable between the Maxigesic® IV, ibuprofen, paracetamol and placebo groups, with the exception of vomiting which was significant for the comparison between Maxigesic® IV and ibuprofen or placebo (but not paracetamol), suggesting that the vomiting reported by patients in the Maxigesic® IV group is attributable to the paracetamol component of the combination, rather than an effect unique to the combination (Table 1).

Table 1: Common treatment–emergent adverse events.

System Organ Class Preferred Term	Maxigesic® IV N=75		Ibuprofen N=76		Paracetamol N=75		Placebo N=50		Total N=276	
	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events
Any Class, Any Term p-value[2]	52 (69.3%)	142	58 (76.3%) 0.365	131	45 (60.0%) 0.305	112	39 (78.0%) 0.312	108	194 (70.3%)	493
Gastrointestinal disorders p-value[2]	29 (38.7%)	66	32 (42.1%) 0.741	49	28 (37.3%) 1.000	47	18 (36.0%) 0.851	28	107 (38.8%)	190
Nausea p-value[2]	22 (29.3%)	37	26 (34.2%) 0.601	33	25 (33.3%) 0.725	28	16 (32.0%) 0.843	22	89 (32.2%)	120
Vomiting p-value[2]	16 (21.3%)	24	5 (6.6%) 0.010	8	11 (14.7%) 0.396	12	1 (2.0%) 0.001	1	33 (12.0%)	45
Nervous system disorders p-value[2]	23 (30.7%)	32	17 (22.4%) 0.273	21	20 (26.7%) 0.718	24	19 (38.0%) 0.442	30	79 (28.6%)	107
Dizziness p-value[2]	13 (17.3%)	18	7 (9.2%) 0.157	8	7 (9.3%) 0.229	8	8 (16.0%) 1.000	10	35 (12.7%)	44
General disorders and administration site conditions p-value[2]	15 (20.0%)	22	17 (22.4%) 0.843	18	8 (10.7%) 0.173	9	13 (26.0%) 0.513	15	53 (19.2%)	64
Skin and subcutaneous tissue disorders p-value[2]	11 (14.7%)	15	15 (19.7%) 0.519	17	10 (13.3%) 1.000	11	7 (14.0%) 1.000	14	43 (15.6%)	57

[1] Incidence > 10% in Total group
[2] Fisher's two-sided exact test with Maxigesic® IV

b. Tabulated summary of adverse reactions

A tabulated summary of TEAEs is presented in Table 2 below. These TEAEs are consistent with the postoperative setting and the use of paracetamol or ibuprofen for analgesia.

Table 2: Tabulated summary of treatment-emergent adverse events (observed in ≥5% of any treatment group).

Preferred Term	Maxigesic® IV N=75		Ibuprofen N=76		Paracetamol N=75		Placebo N=50		Total N=276	
	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events
Nausea	22 (29.3%)	37	26 (34.2%)	33	25 (33.3%)	28	16 (32.0%)	22	89 (32.2%)	120
Vomiting	16 (21.3%)	24	5 (6.6%)	8	11 (14.7%)	12	1 (2.0%)	1	33 (12.0%)	45
Dizziness	13 (17.3%)	18	7 (9.2%)	8	7 (9.3%)	8	8 (16.0%)	10	35 (12.7%)	44
Infusion site pain	10 (13.3%)	15	7 (9.2%)	8	0 (0.0%)	0	1 (2.0%)	1	18 (6.5%)	24
Pruritus	5 (6.7%)	5	4 (5.3%)	4	3 (4.0%)	3	2 (4.0%)	2	14 (5.1%)	14
Somnolence	5 (6.7%)	5	6 (7.9%)	7	6 (8.0%)	7	3 (6.0%)	4	20 (7.2%)	23
Constipation	4 (5.3%)	4	4 (5.3%)	4	4 (5.3%)	4	4 (8.0%)	4	16 (5.8%)	16
Headache	4 (5.3%)	6	5 (6.6%)	5	5 (6.7%)	5	10 (20.0%)	11	24 (8.7%)	27
Hyperhidrosis	2 (2.7%)	2	4 (5.3%)	4	4 (5.3%)	4	3 (6.0%)	4	13 (4.7%)	14
Infusion site extravasation	2 (2.7%)	2	5 (6.6%)	5	2 (2.7%)	2	7 (14.0%)	8	16 (5.8%)	17
Decreased appetite	1 (1.3%)	1	1 (1.3%)	1	4 (5.3%)	4	2 (4.0%)	2	8 (2.9%)	8
Muscle spasms	1 (1.3%)	1	0 (0.0%)	0	1 (1.3%)	1	4 (8.0%)	4	6 (2.2%)	6
Hot flush	0 (0.0%)	0	2 (2.6%)	2	2 (2.7%)	2	3 (6.0%)	3	7 (2.5%)	7

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.

4.9 Overdose

There is a risk of poisoning, particularly in elderly subjects, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving enzyme inducers. Poisoning may be fatal in these cases. Acute overdose with paracetamol may also lead to acute renal tubular necrosis.

Symptoms

Symptoms of paracetamol overdose generally appear within the first 24 hours and comprise of nausea, vomiting, anorexia, pallor and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. Acute renal failure with acute tubular necrosis may develop in the absence of severe liver damage. Cardiac arrhythmias have been reported. Overdose, 7.5 g or more of paracetamol in a single administration in adults, causes cytolytic hepatitis likely to induce complete and irreversible hepatic necrosis, resulting in acute or fulminant hepatic failure, hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death.

Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with decreased prothrombin levels that may appear 12 to 48 hours after administration. Clinical symptoms of liver damage are usually evident initially after two days, and reach a maximum after 4 to 6 days.

The following signs and symptoms have occurred in individuals following an overdose of oral ibuprofen: abdominal pain, nausea, vomiting, drowsiness, dizziness, convulsion, and rarely, loss of consciousness.

Treatment

The Rummack-Matthews nomogram relates plasma levels of paracetamol and the time after oral ingestion to the predicted severity of liver injury. The relation of parental paracetamol levels in overdose to liver toxicity has not been examined. Advice or treatment protocols based on oral paracetamol overdoses may not accurately predict the incidence of liver toxicity or need for antidote therapy in Maxigesic® IV overdose.

Emergency measures:

- Immediate hospitalisation.
- Before beginning treatment, take blood for plasma paracetamol assay, as soon as possible after the overdose.
- Treatment of paracetamol overdose may include the antidote N-acetyl cysteine (NAC) by the IV or oral route. In overdoses of oral paracetamol NAC is administered, if possible, before 10 hours but may give some degree of protection from liver toxicity even after this time. The optimal time for administration of NAC and necessary duration of therapy have not been established for overdoses of Maxigesic® IV.
- Symptomatic treatment.
- Hepatic tests must be carried out at the beginning of treatment and repeated every 24 hours. In most cases hepatic transaminases return to normal in one to two weeks with full restitution of the liver function. In very severe cases, however, liver transplantation may be necessary.

There are no specific measures or known antidote to treat acute ibuprofen overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other Analgesics and Antipyretics, Anilides; ATC code: N02BE51.

Mechanism of action

The precise mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established; it may involve central and peripheral actions.

Ibuprofen's mechanism of action, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Maxigesic® IV possesses anti-inflammatory, analgesic, and antipyretic activity.

Pharmacodynamic effects

In a phase III study in 276 patients with at least moderate pain following bunionectomy surgery, perceptible pain relief occurred within 10 minutes and meaningful pain relief occurred within 75 minutes following the administration of Maxigesic® IV. The peak analgesic effect was obtained at 4 hours, before the pain relief gradually declined to lower levels by 6 hours. Maxigesic® IV has not been studied in the reduction of fever; however, both paracetamol and ibuprofen have antipyretic properties.

Clinical trials

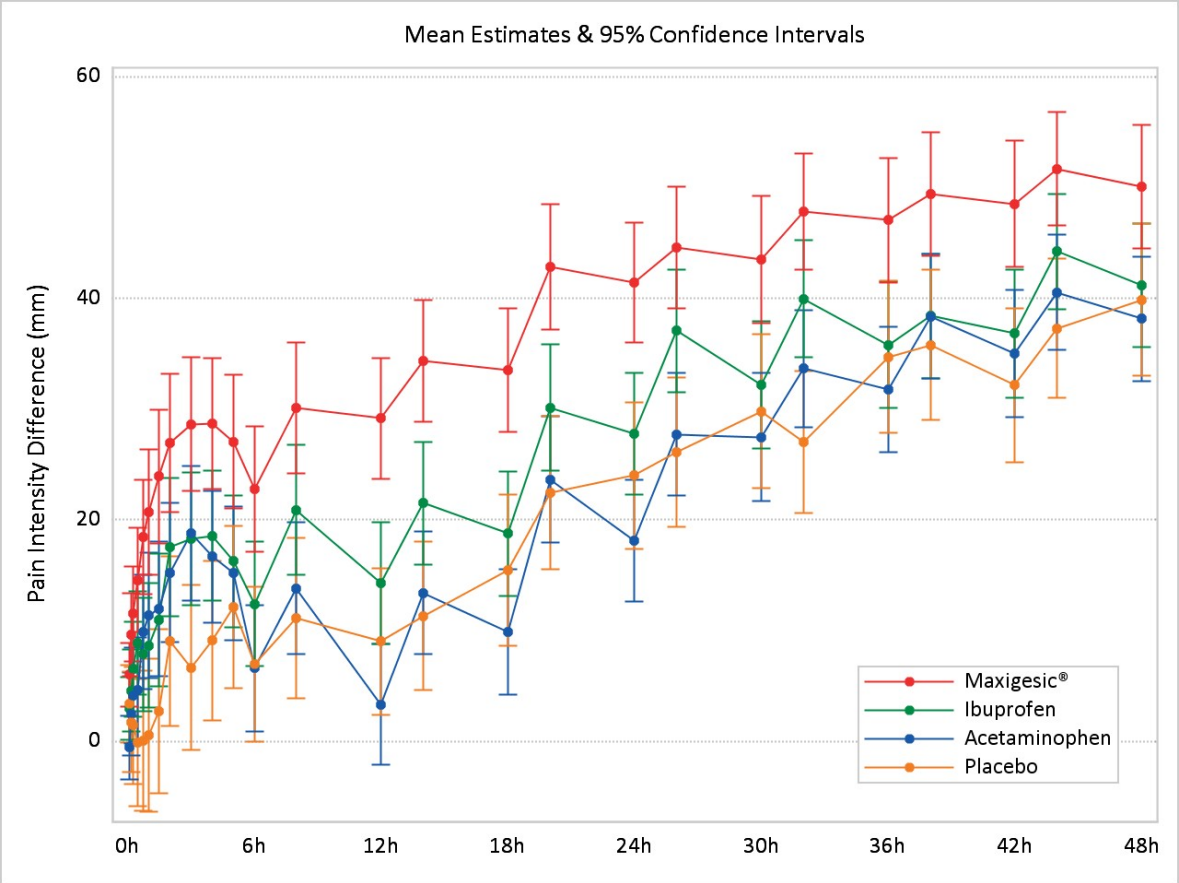
In a phase III efficacy study in 276 patients with at least moderate pain following bunionectomy surgery, the analysis of the primary endpoint, the time-adjusted Summed Pain Intensity Difference (SPID) 0-48 hours, demonstrated that Maxigesic® IV (mean=23.41, SE=2.50) provided more effective pain relief than placebo (mean= - 1.30, SE=3.07), paracetamol (mean=10.42, SE=2.50) or ibuprofen (mean= 9.51, SE=2.49), with a high level of statistical significance ($p<0.001$).

Table 3: Summary of Time-adjusted SPID (0-48 hours) by Treatment Group.

	Maxigesic® IV	**Ibuprofen**	**Paracetamol**	**Placebo**
	N=75	**N=76**	**N=75**	**N=50**
N	75	76	75	50
Mean (SE)	23.41 (2.89)	9.51 (2.53)	10.42 (2.49)	-1.30 (2.08)
Median	23.10	5.40	3.45	-4.00
Min ; Max	-34.08 ; 74.17	-30.68 ; 79.98	-26.78 ; 65.43	-22.42 ; 47.50
Mean Estimate (SE)	23.41 (2.50)	9.51 (2.49)	10.42 (2.50)	-1.30 (3.07)
95% Confidence Interval	18.48 ; 28.34	4.61 ; 14.40	5.49 ; 15.35	-7.33 ; 4.74
Difference Estimate (SE)	-	13.90 (3.53)	12.99 (3.54)	24.71 (3.96)
95% Confidence Interval	-	6.95 ; 20.85	6.02 ; 19.96	16.92 ; 32.50
p-value	-	<0.001	<0.001	<0.001

Figure 1 below shows the pain intensity differences over the 48-hour treatment period. As shown in the Figure, Maxigesic® IV provided generally greater pain relief than placebo, paracetamol and ibuprofen over this period.

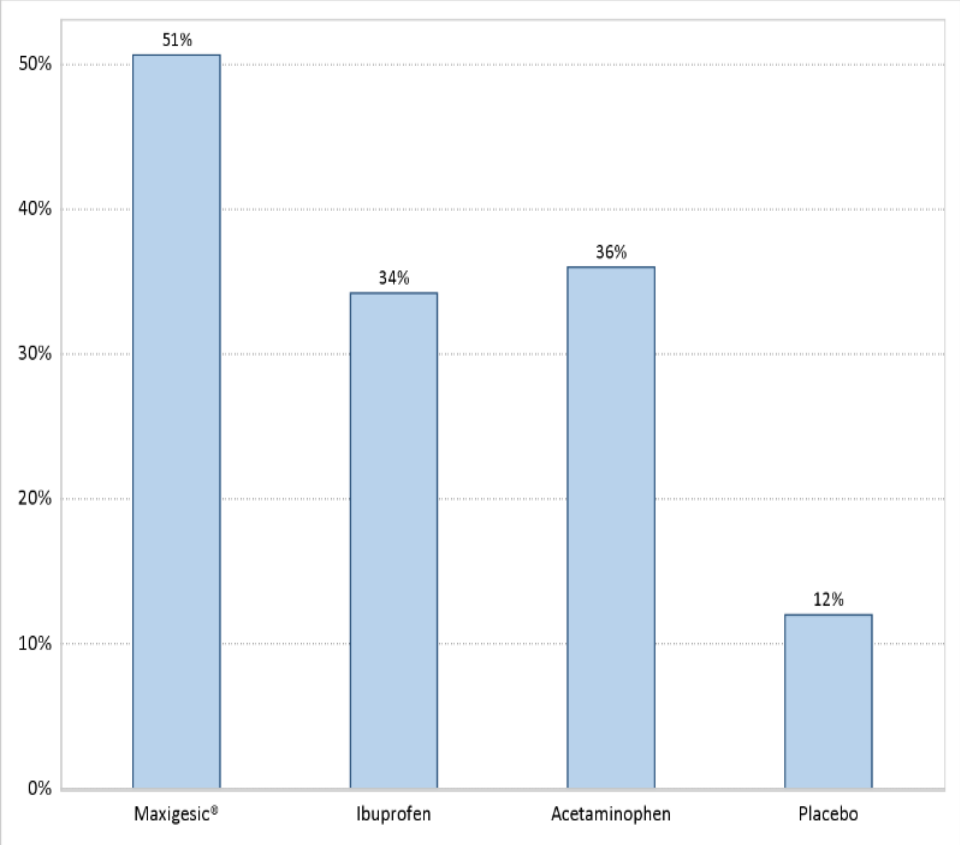
Figure 1: Pain Intensity Differences over the 48 hour treatment period.



Note: Acetaminophen = paracetamol.

The highest response rate was observed in patients treated with Maxigesic® IV, with 51% of patients achieving at least a 50% reduction from baseline pain (Figure 2).

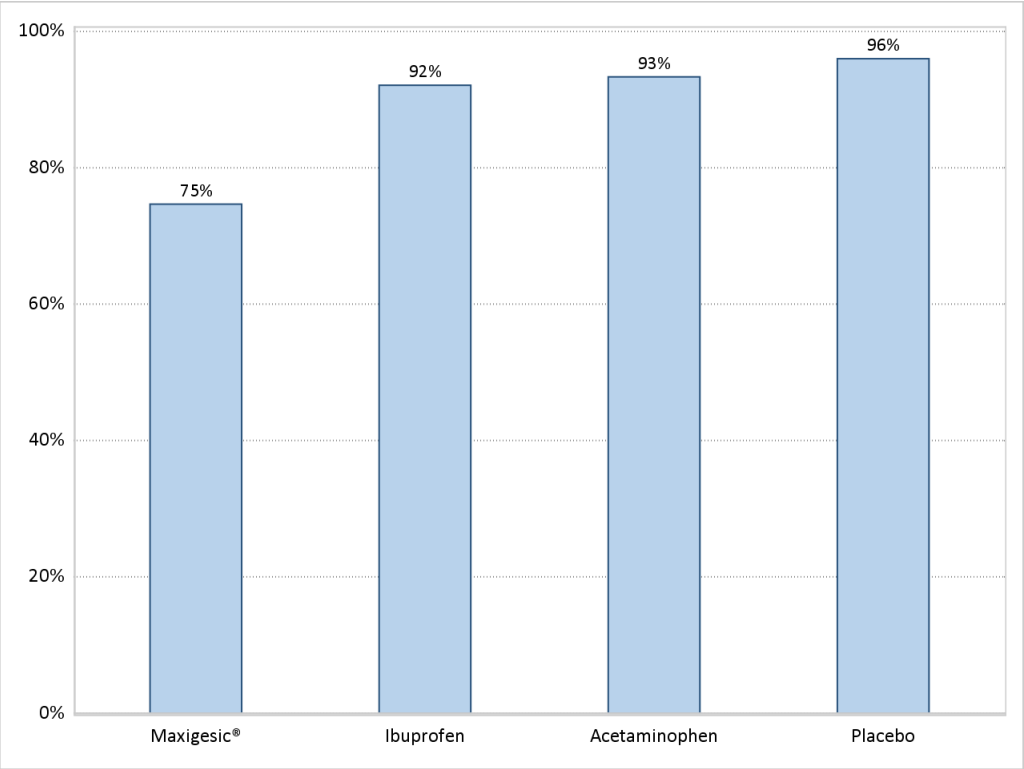
Figure 2: Response rate by treatment group.



Note: Acetaminophen = paracetamol.

Fewer patients in the Maxigesic® IV group (75%) required rescue medication (oxycodone or morphine) compared with 92% of patients in the ibuprofen group, 93% of patients in the placebo group and 96% in the placebo group.

Figure 3: Proportion of patients requiring rescue medication.



Note: Acetaminophen = paracetamol.

Over the entire 48-hour double blind treatment period, the median oral morphine milligram equivalent (MME) of all rescue medication consumed was lowest in the Maxigesic® IV group (30 mg), and lower than consumption in the ibuprofen (43.5 mg, p=0.008), paracetamol (45 mg, p=0.004) and placebo groups (67.5 mg, p<0.001).

5.2 Pharmacokinetic properties

Absorption

Maxigesic® IV is administered as a 15-minute infusion, and the peak plasma concentration of each drug is reached at the end of the infusion. The two active drugs in Maxigesic® IV reach peak plasma levels in the same time frame and have similar plasma half-lives.

The pharmacokinetic parameters of Maxigesic® IV, as determined by a study in 29 healthy volunteers, are presented in Table 4.

Table 4: Mean (SD) pharmacokinetic parameters of paracetamol and ibuprofen in each treatment group.

	Treatment (Mean ± SD)			
Paracetamol	**Maxigesic IV (Treatment A)**	**Paracetamol IV (Treatment B)**	**Maxigesic IV Half dose (Treatment D)**	**Maxigesic Tablets (Treatment E)**
C_{max} (ng/mL)	26709.57 ± 5814.74	26236.06 ± 5430.52	12880.39 ± 2553.15	14907.16 ± 6255.10
AUC_{0-t} (ng.h/mL)	37553.97 ± 9816.96	35846.20 ± 8734.15	18327.40 ± 4758.34	34980.80 ± 9430.21
$AUC_{0-\infty}$ (ng.h/mL)	39419.95 ± 10630.63	37651.43 ± 9454.60	19337.01 ± 5146.46	37023.82 ± 10388.31
T_{max} (h)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.02	0.73 ± 0.42
$t_{1/2}$ (h)	2.39 ± 0.27	2.38 ± 0.25	2.44 ± 0.25	2.51 ± 0.33
Ibuprofen	**Maxigesic IV (Treatment A)**	**Ibuprofen IV (Treatment C)**	**Maxigesic IV Half dose (Treatment D)**	**Maxigesic Tablets (Treatment E)**
C_{max} (ng/mL)	39506.69 ± 6874.06	40292.97 ± 7460.04	20352.05 ± 3090.87	19637.38 ± 5178.29
AUC_{0-t} (ng.h/mL)	73492.69 ± 16509.61	72169.59 ± 15608.70	39642.48 ± 9679.16	70417.75 ± 16260.16
$AUC_{0-\infty}$ (ng.h/mL)	74743.31 ± 17388.69	73410.65 ± 16500.76	40333.88 ± 10240.30	72202.48 ± 17445.46
T_{max} (h)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	1.49 ± 0.89
$t_{1/2}$ (h)	1.88 ± 0.28	1.87 ± 0.27	1.88 ± 0.30	1.99 ± 0.36

Pharmacokinetic parameters were similar following a single dose of Maxigesic® administered either intravenously or orally, except the C_{max} of the intravenous formulation was twice that of the oral formulation and, as expected, the T_{max} following intravenous administration was achieved much faster (in 15 minutes) than with the oral formulation.

The relative bioavailability of paracetamol (93.73%) and ibuprofen (96.60%) confirmed the pharmacokinetic equivalence of the oral and intravenous Maxigesic® formulations.

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 active drugs are metabolized by different pathways and pharmacokinetic studies conducted with Maxigesic® IV confirm that the co-administration of paracetamol and ibuprofen does not alter the pharmacokinetics of either ingredient when administered intravenously or orally.

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 if ibuprofen is in the range of 1.9 to 2 hours.

5.3 Preclinical safety data

In single and repeat-dose toxicity studies conducted in rats, co-administration of paracetamol and ibuprofen at a ratio matching that in Maxigesic® IV (i.e., at a paracetamol-to-ibuprofen ratio of 3.3-to-1) and at dose levels approximately equal to those that patients would receive when using Maxigesic® IV at the maximum recommended dose did not increase the risk of GI or renal toxicity.

The effect of single intravenous or perivenous doses of Maxigesic® IV in an acute local irritation study in male rabbits showed that Maxigesic® IV has little potential to produce local irritation when administered intravenously at the recommended dose level. Moreover when conducting an *in vitro* blood compatibility assessment, no additional haemolysis, plasma protein flocculation/precipitation or platelet aggregation was observed with Maxigesic® IV than with paracetamol IV or ibuprofen IV alone.

Genotoxicity

Paracetamol was not mutagenic in the bacterial mutagenicity assay, but it was clastogenic in mammalian cell assay systems in vitro (mouse TK, human lymphocyte) and in a mouse micronucleus assay *in vivo*. The clastogenic effect was dose-dependent, and the mechanism appears to involve inhibition of replicative DNA synthesis and ribonucleotide reductase at above threshold doses. The clinical significance of clastogenic findings is equivocal as positive findings *in vivo* only occurred at exposures (ca. 8 times the maximum anticipated clinical exposure, based on C_{max}) greater than that for hepatotoxicity, and at doses that were associated with significant cytotoxicity.

Ibuprofen was not mutagenic in bacterial gene mutation assays *in vitro* with or without metabolic activation. A weak positive response was observed in the Sister Chromatid Exchange (SCE) assay in

mouse bone marrow cells at an oral dose of 270 mg/kg and at intraperitoneal doses of 50 and 100 mg/kg, with no-effect at a dose of 25 mg/kg.

Carcinogenicity

No evidence of carcinogenic potential was observed for paracetamol in long-term oral studies in mice (up to 3000 mg/m^2/day, similar to human exposure) and male rats (up to 1800 mg/m^2/day, 0.7 times human exposure). Equivocal evidence of carcinogenic potential (mononuclear cell leukaemia) was observed only in female rats at 1900 mg/m^2/day, or 0.7 times the maximum anticipated clinical exposure on a mg/m^2 basis.

There was no evidence of carcinogenicity in mice and rats treated with ibuprofen orally at respective doses up to 100 mg/kg/day for 80 weeks and 60 mg/kg/day for two years.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cysteine hydrochloride monohydrate Dibasic sodium phosphate dihydrate Mannitol
Hydrochloric acid (for pH adjustment) Sodium hydroxide (for pH adjustment) Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

24 months store below 25°C. or
12 months when store below 30°C.
Do not refrigerate or freeze and protect from light.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze. Protect from light.

6.5 Nature and contents of container

Maxigesic® IV is supplied in 100 mL clear glass vials, closed with a grey rubber stopper and an aluminium flip-off cap, in a pack size of 10 vials. Each vial contains an overfill of solution (between 100.5-104.2 mL) to ensure withdrawal of the label claim.

6.6 Special precautions for disposal

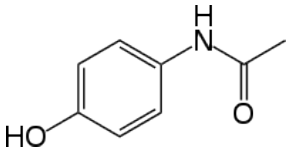
Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Paracetamol

Chemical structure

The chemical name for paracetamol is *N*-(4-hydroxyphenyl)acetamide. It has the following structural formula:



Molecular formula: $C_8H_9NO_2$ Molecular weight: 151.2

Solubility: paracetamol is sparingly soluble in water, freely soluble in alcohol, and very slightly soluble in ether and methylene chloride.

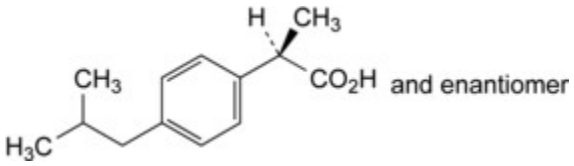
CAS number

103-90-2

Ibuprofen (as sodium dihydrate)

Chemical structure

The chemical name for ibuprofen sodium dihydrate is (2*RS*)-2-[4-(2-methylpropyl)phenyl]propanoic acid sodium dihydrate salt. It has the following structural formula:



Molecular formula: $C_{13}H_{17}O_4Na.2H_2O$ (sodium dihydrate salt) Molecular weight: 206.3 (free acid), 264.3 (sodium dihydrate salt) pKa: 4.43 ± 0.03

Solubility: ibuprofen is very slightly soluble in water (<1 mg/mL) and readily soluble in organic solvents such as ethanol and acetone.

Partition coefficient: n-octanol/water 11.7 at pH 7.4.

CAS number

15687-27-1 (free acid)

527688-20-6 (sodium dihydrate salt)

7. MARKETING AUTHORISATION HOLDER

Alliance Pharma Co Ltd.

128, 1st Floor, Sutthisan Winitchai Road, Samsen Nok, Huai Khwang, Bangkok 10310 Thailand.

8. MARKETING AUTHORISATION NUMBER(S)

Will be updated once obtain the approval

9. DATE OF FIRST APPROVAL

Will be updated once obtain the approval

10. DATE OF REVISION

19 March 2024