SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

(LEXOCAP) Diclofenac sodium 100 mg enteric-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 capsule of LEXOCAP contains: Paracetamol 325 mg, Ibuprofen 200 mg and Caffeine 30 mg
For excipients see section 6.1

3. PHARMACEUTICAL FORM

Capsule
LEXOCAP is a hard gelatin capsule; Cap- light blue with LUEX logo, Body- dark blue with LEXOCAP printing.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Each capsule contains the active ingredients Paracetamol 325 mg, Ibuprofen 200 mg and Caffeine 30 mg. Other inactive ingredients (excipients) are Magnesium Stearate and Purified Talc. Paracetamol is an analgesic (pain killer) and antipyretic (helps to reduce body temperature when you have a fever) and caffeine acts to further help the effectiveness of Paracetamol. Ibuprofen belongs to a group of medicines called NSAID's (non steroidal anti inflammatory drugs). It is an effective analgesic, anti-inflammatory and anti-pyretic.

4.2 Posology and method of administration

Posology

Adults and children 12 years and over:
Take 1 to 2 capsules every 6 hours as required. Lexocap should always be taken with food.

- Do not take more frequently than every 6 hours
- Do not take more than 6 capsules in 24 hours
- Do not give to children under 12 years of age

Avoid drinking too much coffee or tea when taking these capsules.

Method of administration

For oral administration.
To be taken whole with liquid, preferably with or after food.

4.3 Contraindications

Hypersensitivity to paracetamol, Ibuprofen and caffeine, or any of the other constituents.

This product is contraindicated:
• In patients with a known hypersensitivity to ibuprofen, paracetamol or any other excipients in the product.
• In concomitant use with other Paracetamol-containing products – increased risk of serious adverse effects (see Section 4.5).
• In patients with a history of hypersensitivity reactions (e.g. bronchospasm, angioedema, asthma, rhinitis, or urticaria) associated with acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
• In patients with Active, or a history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
• In patients with a history of, or an existing gastrointestinal ulceration/perforation or bleeding, including that associated with NSAIDs (see Section 4.4).
• Patients with defects in coagulation.
• In patients with severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV) (see Section 4.4).
• In concomitant use with other NSAID containing products, including cyclo-oxygenase-2 (COX-2) specific inhibitors and doses of acetylsalicylic acid above 75 mg daily – increased risk of adverse reactions (see Section 4.5).
• During the last trimester of pregnancy due to risk of premature closure of the foetal ductus arteriosus with possible pulmonary hypertension (see Section 4.6)

4.4 Special warnings and precautions for use

Do not exceed the recommended dose.

If symptoms persist consult your doctor.

Keep out of the sight and reach of children.

Paracetamol:

The hazards of paracetamol overdose are greater in patients with non-cirrhotic alcoholic liver disease. Immediate medical advice should be sought in the event of an overdose, even if the patient feels well, because of the risk of delayed, serious liver damage.

Ibuprofen:

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see Section 4.2, and gastrointestinal and cardiovascular risks below) and by patients taking the dose with food.

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Caution is required in patients with certain conditions:

• Respiratory disorders:

In patients suffering from, or with a history of, bronchial asthma or allergic disease NSAIDs have been reported to precipitate bronchospasm.

• SLE and mixed connective tissue disease:

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disease disorders there may be an increased risk of aseptic meningitis (see Section 4.8).

• Cardiovascular and cerebrovascular effects

Appropriate monitoring and medical advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

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 (e.g. myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤1200mg/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 be exercised before initiating long-term treatment for patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) particularly if high doses of ibuprofen (2400 mg/day) are required.

• **Cardiovascular, renal and hepatic impairment:**

The administration of NSAIDs may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see Section 4.3).

• **Gastrointestinal effects:**

NSAIDS should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).

Gastrointestinal (GI) bleeding, ulceration and perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see Section 4.3) and in the elderly. These patients should commence treatment on the lowest dose

available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin selective serotonin-reuptake inhibitors or antiplatelet agents such as acetylsalicylic acid (see Section 4.5).

When GI bleeding or ulceration occurs in patients receiving ibuprofen containing products, the treatment should be withdrawn.

• **Dermatological effects:**

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see Section 4.8). 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. Use of this product should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

• **Impaired female fertility:**

There is limited evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may impair female fertility by an effect on ovulation and is not recommended in women attempting to conceive. This is reversible on withdrawal of treatment. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the product should be considered.

Caffeine:

Apnoea

Apnoea of prematurity is a diagnosis of exclusion. Other causes of apnoea (e.g., central nervous system disorders, primary lung disease, anaemia, sepsis, metabolic disturbances, cardiovascular abnormalities, or obstructive apnoea) should be ruled out or properly treated prior to initiation of treatment with caffeine.

It is advisable to monitor plasma levels of caffeine periodically. However, at the recommended doses, frequent (more than weekly) monitoring of plasma levels is not normally necessary unless there are concerns regarding lack of efficacy or possible toxicity. In premature neonates, caffeine has a prolonged half-life. If higher maintenance dosages are used, the clinician should recognise this potential for accumulation and monitor plasma caffeine levels (see also Section 5.2).

If there is inadequate clinical response to the first loading dose, a second dose may be given, but if there is continued inadequate response, the plasma levels should be confirmed before further doses are given, as the failure to respond could be an indication of another cause of apnoea. Plasma levels should not normally exceed 50 micrograms/ml (optimally 10-30 micrograms/ml).

Caffeine consumption

In newborn infants born to mothers who consumed large quantities of caffeine prior to delivery, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with caffeine, since caffeine readily crosses the placenta into the foetal circulation (see sections 4.2 and 5.2).

Breast-feeding mothers of newborn infants treated with caffeine should not ingest caffeine-containing foods and beverages or medicinal products containing caffeine (see section 4.6), since caffeine is excreted into breast milk (see section 5.2).

Theophylline

In newborns previously treated with theophylline, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with caffeine because preterm infants metabolise theophylline to caffeine.

Seizures

Caffeine is a central nervous system stimulant and seizures have been reported in cases of caffeine overdose. Extreme caution must be exercised if caffeine is used in newborns with seizure disorders.

Cardiovascular reactions

Caffeine has been shown to increase heart rate, left ventricular output, and stroke volume in published studies. Therefore, caffeine should be used with caution in newborns with known cardiovascular disease. There is evidence that caffeine causes tachyarrhythmias in susceptible individuals. In newborns this is usually a simple sinus tachycardia. If there have been any unusual rhythm disturbances on a cardiotocograph (CTG) trace before the baby is born, caffeine should be administered with caution.

Renal and hepatic impairment

Caffeine should be administered with caution in preterm newborn infants with impaired renal or hepatic function. In a post-authorisation safety study, the frequency of adverse reactions in a small number of very premature infants with renal/hepatic impairment appeared to be higher as compared to premature infants without organ impairment (see sections 4.2, 4.8 and 5.2). Doses should be adjusted by monitoring of caffeine plasma concentrations to avoid toxicity in this population.

Necrotising enterocolitis

Necrotising enterocolitis is a common cause of morbidity and mortality in premature newborn infants. There are reports of a possible association between the use of methylxanthines and development of necrotising enterocolitis. However, a causal relationship between caffeine or other methylxanthine use and necrotising enterocolitis has not been established. As for all preterm infants, those treated with caffeine should be carefully monitored for the development of necrotising enterocolitis (see section 4.8).

Caffeine should be used with caution in infants suffering gastro-oesophageal reflux, as the treatment may exacerbate this condition.

Caffeine causes a generalised increase in metabolism, which may result in higher energy and nutrition requirements during therapy.

4.5 Interaction with other medicinal products and other forms of interaction

This product (like any other paracetamol containing products) is contraindicated in combination with other paracetamol containing products – increased risk of serious adverse effects (see Section 4.3).

This product (like any other ibuprofen containing products and NSAIDs) is contraindicated in combination with:

• Acetylsalicylic acid: Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects, unless low-dose acetylsalicylic acid (not above 75 mg daily) has been advised by a doctor (see Section 4.4).

• Experimental data suggest that Ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1)

• Other NSAIDs including cyclo-oxygenase-2 selective inhibitors as these may increase the risk of adverse effects (see Section 4.3).

This product (like any other paracetamol containing products) should be used with caution in combination with:

• Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour if maximal analgesia is required.

• Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

• Warfarin: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

This product (like any other ibuprofen containing products and NSAIDs) should be used with caution in combination with:

• Anticoagulants: NSAIDs may enhance the effects of anticoagulants, i.e. warfarin (see section 4.4).

• Antihypertensives (ACE inhibitors and Angiotensin II Antagonists) and diuretics: NSAIDs may reduce the effects of these drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking a coxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics may increase the risk of nephrotoxicity of NSAIDs.

• Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see Section 4.4).

• Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

• Ciclosporin: Increased risk of nephrotoxicity.

• Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see Section 4.4).

• Lithium: Decreased elimination of lithium.

• Methotrexate: Decreased elimination of methotrexate.

• 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.

• Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

• Zidovudine: Increased risk of haematological toxicity with 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.

This product (like any other caffeine containing products):

Has the potential to interact with active substances that are substrates for CYP1A2, inhibit CYP1A2, or induce CYP1A2. Cytochrome P450 1A2 (CYP1A2) is the major enzyme involved in the metabolism of caffeine in humans. However, caffeine metabolism in preterm newborn infants is limited due to their immature hepatic enzyme systems.

Interconversion between caffeine and other xanthines such as theophylline has been reported in premature neonates. Therefore the concurrent use of these drugs should be avoided. Baseline serum levels of caffeine should be measured in patients previously treated with theophylline.

Although few data exist on interactions of caffeine with other active substances in preterm newborn infants, lower doses of caffeine may be needed following co-administration of active substances which are reported to decrease caffeine elimination in adults (e.g., cimetidine and ketoconazole) and higher caffeine doses may be needed following co-administration of active substances that increase caffeine elimination (e.g., phenobarbital and phenytoin). Where doubt exists about possible interactions, plasma caffeine concentrations should be measured.

As bacterial overgrowth in the gut is associated with the development of necrotising enterocolitis, co-administration of caffeine with medicinal products that suppress gastric acid secretion (antihistamine H2 receptor blockers or proton-pump inhibitors) may in theory increase the risk of necrotising enterocolitis (see section 4.4 and 4.8).

Concurrent use of caffeine and doxapram might potentiate their stimulatory effects on the cardio-respiratory and central nervous system. If concurrent use is indicated, cardiac rhythm and blood pressure must be carefully monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There is no experience of use of this product in humans during pregnancy.

Congenital abnormalities have been reported in association with NSAID administration in man; however these are low in frequency and do not appear to follow any discernible pattern. In view

of the known affects of NSAIDs on the foetal cardiovascular system (risk of closure of ductus arteriosus), use in the last trimester is contraindicated. The onset of labour may be delayed and duration increased with an increased bleeding tendency in both mother and child (see Section 4.3). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol use at the recommended dosage.

Therefore if possible, the use of this product should be avoided in the first six months of pregnancy and contraindicated in the last three months of pregnancy (see Section 4.3).

Lactation:

Ibuprofen and its metabolites can pass in very small amounts (0.0008% of the maternal dose) into the breast milk. No harmful effects to infants are known.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding.

For Caffeine;

Fertility

Effects on reproductive performance observed in animals are not relevant to its indication in the preterm newborn infants (see section 5.3).

Pregnancy

Caffeine in animal studies, at high doses, was shown to be embryotoxic and teratogenic. These effects are not relevant with regard to short term administration in the preterm infant population (see section 5.3).

Breast-feeding

Caffeine is excreted into breast milk and readily crosses the placenta into the foetal circulation (see section 5.2).

Breast-feeding mothers of newborn infants treated with caffeine citrate should not ingest caffeine-containing foods, beverages or medicinal products containing caffeine.

In newborn infants born to mothers who consumed large quantities of caffeine prior to delivery, baseline plasma caffeine concentrations should be measured prior to initiation of treatment with caffeine citrate (see section 4.4).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical trials with this product have not indicated any other undesirable effects other than those for ibuprofen or paracetamol alone.

The following table lists adverse effects from pharmacovigilance data experienced by patients taking ibuprofen alone or paracetamol alone in short-term and long-term use.

Adverse events which have been associated with Ibuprofen alone or Paracetamol alone are given below, tabulated by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

System Organ Class	Frequency	Adverse Event
Blood and Lymphatic System Disorders	Very rare	Haematopoietic disorders[1]
Immune System Disorders	Uncommon	Hypersensitivity with urticaria and pruritus[2]
	Very rare	Severe hypersensitivity reactions. Symptoms can include facial, tongue and throat swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock)[2]
Psychiatric Disorders	Very rare	Confusion, depression and hallucinations
Nervous System Disorders	Uncommon	Headache and dizziness
	Very rare	Aseptic meningitis[3], paraesthesia, optic neuritis and somnolence
Eye Disorders	Very rare	Visual disturbance
Ear and Labyrinth Disorders	Very rare	Tinnitus and vertigo

Cardiac Disorders	Very rare	Cardiac failure and oedema[4]
Vascular Disorders	Very rare	Hypertension[4]
Respiratory and thoracic and mediastinal disorders	Very rare	Respiratory reactivity including: asthma, exacerbation of asthma, bronchospasm and dyspnoea[2]
Gastrointestinal Disorders	Common	Abdominal pain, vomiting, diarrhoea, nausea, dyspepsia and abdominal discomfort[5]
	Uncommon	peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena, haematemesis[6], mouth ulceration, exacerbation of colitis and Crohn's disease[7] gastritis, pancreatitis, flatulence and constipation
Hepatobiliary Disorders	Very rare	Abnormal liver function, hepatitis and jaundice[8]
Skin and Subcutaneous Tissue Disorders	Common	Hyperhidrosis
	Uncommon	Various skin rashes[2]
	Very rare	Bullous reactions including Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis[2].Exfoliative dermatoses, purpura, photosensitivity
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)
Renal and Urinary Disorders	Very rare	Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, and acute and chronic renal failure[9]
General Disorders and Administration Site Conditions	Very rare	Fatigue and malaise
Investigations	Common	Alanine aminotransferase increased, gamma-glutamyltransferase increased and liver function

		tests abnormal with paracetamol. Blood creatinine increased, blood urea increased.
	Uncommon	Aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinease increased, haemoglobin decreased and platelet count increased.

Description of Selected Adverse Reactions

Examples include agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia leucopenia, neutropenia, pancytopenia and thrombocytopenia.

First signs are fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising and nose bleeding.

Hypersensitivity reactions have been reported. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract activity, e.g. asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) various skin reactions, including rashes of various types, pruritus, urticaria, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses (including toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme).

The pathogenic mechanism of drug-Induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, Single cases of aseptic meningitis in patients with existing autoimmune disorders (such as systemic lupus erythematosus and mixed connective tissue disease) during treatment with Ibuprofen, with symptoms such as: stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (see Section 4.4).

Clinical studies suggest that use of ibuprofen particularly at high a dose (2400mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

The adverse events observed most often are gastrointestinal in nature.

Sometimes fatal, particularly in the elderly.

See section 4.4.

In overdose Paracetamol can cause acute hepatic failure, hepatic failure, hepatic necrosis and liver injury (see Section 4.9).

Especially in long-term use, associated with increased serum urea and oedema.

Also includes papillary necrosis.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Summary of the safety profile for caffeine containing product

Effects described include central nervous system (CNS) stimulation such as convulsion, irritability, restlessness and jitteriness, cardiac effects such as tachycardia, arrhythmia, hypertension and increased stroke volume, metabolism and nutrition disorders such as hyperglycaemia. These effects are dose related and may necessitate measurement of plasma levels and dose reduction.

They are generally, although not exclusively, associated with serum caffeine concentrations ≥50micrograms/ml.

Tabulated list of adverse reactions

The adverse reactions described in the short- and long-term published literature and obtained from a post-authorisation safety study that can be associated with caffeine citrate are listed below by System Organ Class and Preferred Term (MedDRA).

Frequency is defined as: very common (≥ 1/10), common (≥1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	Adverse Reaction	Frequency
Infections and infestations	Sepsis	Not known
Immune system disorders	Hypersensitivity reaction	Rare
Metabolism and nutrition disorders	Hyperglycaemia	Common
	Hypoglycaemia, failure to thrive, feeding intolerance	Not known
Nervous system disorders	Convulsion	Uncommon
	Irritability, jitteriness, restlessness, brain injury	Not known
Ear and labyrinth disorders	Deafness	Not known
Cardiac disorders	Tachycardia	Common
	Arrhythmia	Uncommon
	Increased left ventricular output and increased stroke volume	Not known
Gastrointestinal disorders	Regurgitation, increased gastric aspirate, necrotising enterocolitis	Not known
General disorders and administration site conditions	Infusion site phlebitis, infusion site inflammation	Common
Investigations	Urine output increased, urine sodium and calcium increased, haemoglobin decreased, thyroxine	Not known

	decreased	

Description of selected adverse reactions

Necrotising enterocolitis is a common cause of morbidity and mortality in premature newborn infants. There are reports of a possible association between the use of methylxanthines and development of necrotising enterocolitis. However, a causal relationship between caffeine or other methylxanthine use and necrotising enterocolitis has not been established.

In a double-blind placebo-controlled study of caffeine citrate in 85 preterm infants (see section 5.1), necrotising enterocolitis was diagnosed in the blinded phase of the study in two infants on active treatment and one on placebo, and in three infants on caffeine during the open-label phase of the study. Three of the infants who developed necrotising enterocolitis during the study died. A large multicentre study (n=2006) investigating long-term outcome of premature infants treated with caffeine citrate (see section 5.1) did not show an increased frequency of necrotising enterocolitis in the caffeine group when compared to placebo. As for all preterm infants, those treated with caffeine citrate should be carefully monitored for the development of necrotising enterocolitis (see section 4.4). Brain injury, convulsion and deafness were observed but they were more frequent in the placebo group.

Caffeine may suppress erythropoietin synthesis and hence reduce haemoglobin concentration with prolonged treatment.

Transient falls in thyroxine (T4) have been recorded in infants at the start of therapy but these are not sustained with maintained therapy.

Available evidence does not indicate any adverse long-term reactions of neonatal caffeine therapy as regards neurodevelopmental outcome, failure to thrive or on the cardiovascular, gastrointestinal or endocrine systems. Caffeine does not appear to aggravate cerebral hypoxia or to exacerbate any resulting damage, although the possibility cannot be ruled out.

Other special populations

In a post-authorisation safety study on 506 preterm infants treated with Peyona, safety data have been collected in 31 very premature infants with renal/hepatic impairment. Adverse reactions appeared to be more frequent in this subgroup with organ impairment than in other observed infants without organ impairment. Cardiac disorders (tachycardia, including one single case of arrhythmia) were mostly reported.

4.9 Overdose

Paracetamol

Liver damage is possible in adults who have taken 10 g (equivalent to 20 tablets) or more of paracetamol. Ingestion of 5 g (equivalent to 10 tablets) or more of paracetamol may lead to liver damage if the patient has one or more of the risk factors below:

a) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

b) Regularly consumes alcohol in excess of recommended amounts.

c) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Symptoms

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

Management

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

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

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol however; the maximum protective effect is obtained up to 8 hours post ingestion. The effectiveness of the antidote declines sharply after this time.

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

Patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be managed in accordance with established guidelines.

Ibuprofen

In children ingestion of more than 400 mg/kg of Ibuprofen may cause symptoms. In adults the dose response effect is less clear cut.

The half-life in overdose is 1.5-3 hours.

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or

coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time / INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur if there is a co-incident of dehydration. Exacerbation of asthma is possible in asthmatics.

Management

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

Caffeine

Symptoms

Common features include CNS stimulation; anxiety, nervousness, restlessness, insomnia, excitement, muscle twitching, confusion, convulsions.

Cardiac Symptoms include tachycardia, cardiac arrhythmia. Gastric symptoms include abdominal or stomach pains.

Other symptoms of overdosage, associated with the caffeine component, include diuresis and facial flushing.

Management

Treatment of caffeine overdose is primarily symptomatic and supportive. Diuresis should be treated by maintaining fluid and electrolyte balance and CNS symptoms can be controlled by intravenous administration of diazepam.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC Code: M01AE51 – Musculoskeletal system, anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives. Ibuprofen combinations.

The pharmacological actions of ibuprofen and paracetamol differ in their site and mode of action. These complementary modes of action are synergistic which results in greater antinociception and antipyresis than the single actives alone.

Ibuprofen is an NSAID that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. Prostaglandins sensitise nociceptive afferent nerve terminals to mediators such as bradykinin. Ibuprofen therefore elicits an analgesic effect through peripheral inhibition of the cycloxygenase-2 (COX-2) isoenzyme with a subsequent reduction in sensitisation of nociceptive nerve terminals. Ibuprofen has also been shown to inhibit induced-leucocyte migration into inflamed areas. Ibuprofen has a pronounced action within the spinal cord due, in part, to the inhibition of COX. Ibuprofen's antipyretic effects are produced by the central inhibition of prostaglandins in the hypothalamus. Ibuprofen reversibly inhibits platelet aggregation. In humans, ibuprofen reduces inflammatory pain, swellings and fever.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

Paracetamol's exact mechanism of action is still not completely defined; however there is considerable evidence to support the hypothesis of a central antinociceptive effect. Various

biochemical studies point to inhibition of central COX-2 activity. Paracetamol may also stimulate the activity of descending 5-hydroxytryptamine (serotonin) pathways that inhibit nociceptive signal transmission in the spinal cord. Evidence has shown that paracetamol is a very weak inhibitor of peripheral COX-1 and 2 isoenzymes.

The clinical efficacy of ibuprofen and paracetamol has been demonstrated in pain associated with headache, toothache and dysmenorrhoea, and fever; furthermore efficacy has been shown in patients with pain and fever associated with cold and influenza and in pain models such as sore throat, muscular pain or soft tissue injury and backache.

This product is especially suitable for pain which requires stronger pain relief than ibuprofen 400 mg or paracetamol 1000 mg alone, and faster pain relief than ibuprofen.

Summary of 2 tablet clinical data

A randomised, double-blind placebo-controlled studies were conducted with the combination using the acute pain model of post-operative dental pain. The studies show that:

• This product provides more effective pain relief than paracetamol 1000 mg ($p<0.0001$) and ibuprofen 400 mg ($p< 0.05$) which are clinically and statistically significant.

• This product has a fast onset of action with 'confirmed perceptible pain relief' achieved in a median of 18.3 minutes. The onset of action was significantly more rapid than for ibuprofen 400 mg (23.8 minutes, $p=0.0015$). 'Meaningful pain relief' for this product was achieved in a median of 44.6 minutes, which was significantly faster than for ibuprofen 400 mg (70.5 minutes, $p<0.0001$)..

• Duration of analgesia was significantly longer for this product (9.1 hours) compared to paracetamol 500 mg (4 hours) or 1000 mg (5 hours).

• The global evaluation of the study medication by the subjects showed high levels of satisfaction with 93.2% rating the product as 'good', 'very good' or 'excellent' in achieving pain relief. The fixed combination product performed significantly better than paracetamol 1000 mg ($p<0.0001$).

A randomised, double-blind controlled clinical study was conducted with the product in the treatment of chronic knee pain. The study showed that:

• The product provides more effective pain relief than paracetamol 1000 mg in short-term treatment ($p<0.01$) and long term treatment ($p<0.01$).

• The global evaluation of the product by the subjects showed high levels of satisfaction with 60.2% rating the product as 'good' or 'excellent' as a long term treatment for a painful knee. The product performed significantly better than paracetamol 1000 mg ($p<0.001$).

Caffeine

Mechanisms of action/effect

Central nervous system stimulant – caffeine stimulates all levels of the CNS, although its cortical effects are milder and of shorter duration than those of amphetamines.

Analgesia adjunct

Caffeine constricts cerebral vasculature with an accompanying decrease in the cerebral blood flow and in the oxygen tension of the brain. It is believed that caffeine helps to relieve headache by providing more rapid onset of action and/or enhanced pain relief with lower doses of analgesic. Recent studies with ergotamine indicate that the enhancement of effect by the addition of caffeine may also be due to improved gastrointestinal absorption of ergotamine when administered with caffeine.

5.2 Pharmacokinetic properties

Ibuprofen is well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Plasma levels of ibuprofen from this product are detected from 5 minutes with peak plasma concentrations achieved within 1-2 hours after ingestion on an empty stomach. When this product was taken with food peak ibuprofen plasma levels were lower and delayed by a median of 25 minutes, but overall extent of absorption was equivalent.

Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete. The elimination half-life is approximately 2 hours.

In limited studies, ibuprofen appears in the breast milk in very low concentrations.

No significant differences in ibuprofen pharmacokinetic profile are observed in the elderly.

Paracetamol is readily absorbed from the gastrointestinal tract. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose-dependent. Plasma levels of paracetamol from this product are detected from 5 minutes with peak plasma concentrations occurring at 0.5-0.67 hours after ingestion on an empty stomach. When this product was taken with food peak paracetamol plasma levels were lower and delayed by a median of 55 minutes, but overall extent of absorption was equivalent.

Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates, with about 10% as glutathione conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life is approximately 3 hours.

A minor hydroxylated metabolite, which is usually produced in very small amounts by mixed function oxidases in the liver and detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdose and cause liver damage.

No significant differences in the paracetamol pharmacokinetic profile are observed in the elderly.

The bioavailability and pharmacokinetic profiles of ibuprofen and paracetamol taken as this product are not altered when taken in combination as a single or repeat dose.

This product is formulated using a technology which releases both Ibuprofen and Paracetamol simultaneously, so that the active ingredients deliver a combination effect.

Caffeine

Absorption and fate

Caffeine is completely and rapidly absorbed after oral administration with peak concentrations occurring between 5 and 90 minutes after dose in fasted subjects. There is no evidence of presystemic metabolism. Elimination is almost entirely by hepatic metabolism in adults.

In adults, marked individual variability in the rate of elimination occurs. The mean plasma elimination half-life is 4.9 hours with a range of 1.9 - 12.2 hours. Caffeine distributes into all body fluids. The mean plasma protein binding of caffeine is 35%.

Caffeine is metabolised almost completely via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine). Minor metabolites include 1-methylacrylic acid and 5-acethylamine-6-formylamine-3-methyluracil (AFMU).

5.3 Preclinical safety data

The toxicological safety profile of ibuprofen and paracetamol has been established in animal experiments and in humans from extensive clinical experience. There are no new preclinical data of relevance to the prescriber which are additional to the data already presented in this Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Magnesium Stearate
Purified Talc

6.2. Incompatibilities

Not applicable

6.3. Shelf Life

3 years. Store in a cool dry place below 25ºC

6.4. Special Precautions for Storage

No special precautions for storage.
For storage conditions of the medicinal product, see Section 6.3

6.5. Nature and Contents of Container

LEXOCAP capsules

LEXOCAP is a hard gelatin capsule; Cap- light blue with LUEX logo, Body- dark blue with LEXOCAP printing.10 capsules are packed in PVC/aluminum foil blisters and these blisters are packed in printed inner cartons along with an insert. 10 inner cartons are packed in outer cartons.

6.6. Instructions for Use and Handling

No special requirements

7. APPLICANT / SUPPLIER

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Address: 17, Dadeban Rd. North Industrial Area (Next to SSB), P. O. Box 15146. Accra

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8. FDA APPLICATION NUMBER

N/A

9. DATE OF RENEWAL OF REGISTRATION

20th May, 2020

10. DATE OF REVISION OF THE TEXT

May, 2020