

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen 600 mg Film Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 600mg ibuprofen.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pink capsule shaped, biconvex 22 x 10 mm, film coated tablets marked with “LPC I 600” on one side and decorative scoreline on the other.

The score line is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ibuprofen is indicated for its analgesic and anti-inflammatory effect in rheumatoid arthritis (including juvenile rheumatoid arthritis or Still’s disease) ankylosing spondylitis, osteoarthritis and other non-rheumatoid arthropathies. In non-articular rheumatoid conditions, ibuprofen is indicated in periarticular conditions e.g. frozen shoulder, bursitis, tendinitis, tenosynovitis and low back pain.

Ibuprofen can be used in soft-tissue injuries, e.g. sprains and strains. It is also indicated for the relief of mild to moderate pain, e.g. dental and postoperative pain and dysmenorrhoea.

It is also indicated for the relief of migraine.

4.2 Posology and method of administration

Posology:

The lowest effective dose should be used for the shortest time necessary to relieve symptoms (see section 4.4). The patient should consult a doctor if symptoms persist or worsen, or if the product is required for more than 10 days.

Adults:

Initial dosage is 1800 mg daily in divided doses. Some patients can be maintained on 600 -1800 mg daily. In severe or acute conditions it may be advantageous to increase the dosage provided that the total daily dosage does not exceed 2400 mg in divided doses.

Elderly:

The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

Children:

Ibuprofen 600 mg tablets are not suitable for children.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

For infants aged 3 - 5 months medical advice should be sought if symptoms worsen or not later than 24 hours if symptoms persist.

If in children and in adolescents this medical product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

Method of administration:

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Ibuprofen should not be used in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) after taking ibuprofen, aspirin or other NSAIDs.
- Ibuprofen is also contraindicated in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Ibuprofen should not be used in patients with active or history of recurrent peptic ulcer

or gastrointestinal haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

- Ibuprofen should not be given to patients with conditions involving an increased tendency to bleeding.
- Ibuprofen is contraindicated in patients with severe heart failure (NYHA Class IV), hepatic failure and renal failure (see section 4.4).
- Ibuprofen is contraindicated during last trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

As with other NSAIDs, ibuprofen may mask the signs of infection.

The use of ibuprofen product with concomitant NSAIDs including cyclo-oxygenase-2 specific inhibitors should be avoided due to the increased risk of ulceration or bleeding (See section 4.5).

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

Paediatric population

There is a risk of renal impairment in dehydrated children and adolescents.

Respiratory disorders and hypersensitivity reactions:

Caution is required if Ibuprofen is administered to patients suffering from or with a previous history of bronchial asthma, chronic rhinitis or allergic disorders, since NSAIDs have been reported to precipitate bronchospasm, urticarial or angioedema in such patients. The possibility of cross-sensitivity with aspirin and other NSAIDs should be borne in mind.

SLE and mixed connective tissue disease:

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

Renal effects:

Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration.

As with other NSAIDs, long-term administration of ibuprofen has resulted in renal papillary necrosis and other renal pathologic changes. 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 an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may cause renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors and the elderly.

Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

Renal tubular acidosis and hypokalaemia may occur following acute overdose and in patients taking ibuprofen products over long periods at high doses (typically greater than 4 weeks), including doses exceeding the recommended daily dose.

Cardiac, renal and hepatic impairment:

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. The habitual concomitant intake of various similar painkillers further increases this risk. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. For these patients, use the lowest effective dose, for the shortest possible duration and monitor renal function especially in long-term treated patients (see also section 4.3).

Ibuprofen should be given with care to patients with a history of heart failure or hypertension since oedema has been reported in association with Ibuprofen administration

There is a risk of renal impairment in dehydrated children and adolescents.

Cardiovascular and cerebrovascular effects:

Appropriate monitoring and 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.

Cases of Kounis syndrome have been reported in patients treated with Ibuprofen tablets. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

Clinical studies suggest that use of ibuprofen, particularly at high doses (2400 mg/day) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events such as 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, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Impaired female fertility:

The use of ibuprofen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or

who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered.

Gastrointestinal bleeding, ulceration and perforation:

GI bleeding, ulceration or 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 aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

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

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity, ulceration or bleeding, such as oral corticosteroids, or anticoagulants such as warfarin (prothrombin time should be monitored daily for the first few days of combined treatment), selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

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

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).

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome) have been reported very rarely in association with the use of ibuprofen (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy, the onset of the reaction occurring within the first month of treatment in the majority of cases. Acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, has been reported in relation to ibuprofen-containing products. If signs and symptoms suggestive of these reactions appear ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate).

Haematological effects

Ibuprofen, like other NSAIDs, can interfere with platelet aggregation and prolong bleeding time in normal subjects.

Aseptic meningitis

Aseptic meningitis has been observed on rare occasions in patients on 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 an underlying chronic disease

Treatment should be discontinued in patients reporting blurred or diminished vision, scotomata and /or changes in colour vision.

Masking of symptoms of underlying infections

Ibuprofen Tablets can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Ibuprofen Tablet is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In nonhospital settings, the patient should consult a doctor if symptoms persist or worsen.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should not be used in combination with:

Aspirin (Acetylsalicylic Acid): As with other products containing NSAIDs, concomitant administration of ibuprofen and aspirin (unless low-dose aspirin not above 75 mg daily) has been advised by a doctor), is not generally recommended because of the potential of increase adverse effects such as gastrointestinal side effects and toxicity including ulceration or haemorrhage (see section 4.3 and 4.4)

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin (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 analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs, including Cox – inhibitors, as this may increase the risk of adverse effects (see section 4.4)

Ibuprofen should be used with caution in combination with:

Aminoglycosides: NSAIDs may decrease the excretion of aminoglycosides. Increased renal toxicity has been reported in patients receiving concomitant ibuprofen and aminoglycoside therapy.

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin and heparin (see section 4.4).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding with NSAIDs (see section 4.4).

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

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

Ciclosporin: Increased risk of nephrotoxicity.

Corticosteroids: Increased risk of GI bleeding (see section 4.4).

Antihypertensives, beta-blockers and diuretics: NSAIDs may diminish the effect of anti-hypertensives, such as ACE inhibitors, angiotensin-II receptor antagonists, beta-blockers and diuretic. They may increase risk of hyperkalaemia with potassium-sparing diuretics and may also antagonise thiazides and reduce anti-hypertensive effect of furosemide. Diuretics can also increase the risk of nephrotoxicity of NSAIDs..

Lithium: Decreased elimination of lithium.

Methotrexate: NSAIDs may inhibit the tubular secretion of methotrexate and reduce clearance of methotrexate.

Mifepristone: A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of NSAIDs. Limited evidence suggests that coadministration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medicinal termination of pregnancy.

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.

Sulphonylureas: Ibuprofen may potentiate the effects of sulphonylurea medications. There have been rare reports of hypoglycaemia in patients on sulphonylurea medications receiving ibuprofen.

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

Phenytoin Sodium: Phenytoin concentration and toxicity have been increased by Ibuprofen.

Zidovudine: There is evidence of an increased risk of haemarthroses and

haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen. Increased risk of haematological toxicity when NSAIDs are given with zidovudine.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

From the 20th week of pregnancy onward, ibuprofen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to ibuprofen for several days from gestational week 20 onward. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy (see section 4.3).

Breast-feeding:

In limited studies so far available, NSAIDs can appear in the breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

Fertility:

See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

When used as monotherapy metformin hydrochloride does not influence the ability to drive or operate machinery. However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulphonylureas, insulin, or meglitinides).

Patients undergoing such combination therapy should be warned about the possible adverse effects of hypoglycaemia.

4.8. Undesirable effects

Gastrointestinal disorders: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, gastrointestinal haemorrhage and exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following ibuprofen administration. Less frequently, gastritis, duodenal ulcer, gastric ulcer and gastrointestinal perforation have been observed.

Immune system disorders: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reaction and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, very rarely, erythema multiforme, bullous dermatoses (including Stevens- Johnson syndrome and toxic epidermal necrolysis).

Cardiac disorders and vascular disorders: Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical studies suggest that

use of ibuprofen, particularly at high dose (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events such as myocardial infarction or stroke (see section 4.4).

Infections and infestations: Rhinitis and aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4).

Exacerbation of infection-related inflammations coinciding with the use of NSAIDs has been described. If signs of an infection occur or get worse during use of Ibuprofen the patient is therefore recommended to go to a doctor without delay.

Skin and subcutaneous tissue disorders: In exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection (see also "Infections and infestations")

The following adverse reactions possibly related to ibuprofen and displayed by MedDRA frequency convention and system organ classification. Frequency groupings are classified according to the subsequent conventions: very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very rare ($< 1/10,000$) and Not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Events
Gastrointestinal Disorders	Common	Dyspepsia, diarrhoea, nausea, vomiting, abdominal pain, flatulence, constipation, melaena, haematemesis, gastrointestinal haemorrhage
	Uncommon:	Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation
	Very rare:	Pancreatitis
	Not Known	Exacerbation of ulcerative colitis and Crohn's disease.
Infections and infestations	Uncommon	Rhinitis
	Rare	Meningitis aseptic (see section 4.4)
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia
Psychiatric disorders	Uncommon	Insomnia, anxiety
	Rare	Depression, confusional state
Nervous System Disorders	Common	Headache, dizziness
	Uncommon:	Paraesthesia, somnolence, drowsiness
	Rare	Optic neuritis.
Eye disorders	Uncommon	Visual impairment

	Rare	Toxic optic neuropathy
Ear and labyrinth disorders	Uncommon	Hearing impaired, tinnitus, vertigo
Respiratory, thoracic and mediastinal disorders	Uncommon	Asthma, bronchospasm, dyspnoea
Cardiac Disorders	Very rare	Cardiac failure, myocardial infarction (also see section 4.4)
	Not known	Kounis syndrome
Vascular Disorders	Very rare	Hypertension
Metabolism and Nutrition Disorders	Not known	Decreased Appetite Hypokalaemia*
Renal and Urinary Disorders	Uncommon	Nephrotoxicity in various forms e.g. renal failure, tubulointerstitial nephritis, nephrotic syndrome, papillary necrosis, especially in long term use, associated with increased serum urea and oedema. Haematuria. Fluid retention may rarely precipitate congestive heart failure in elderly patients.
	Very rare	Acute renal failure
	Not Known	Ureteric colic, dysuria, Renal tubular acidosis*, Renal insufficiency
General disorders administration site conditions	Common	Fatigue
	Rare	Oedema
Hepatobiliary Disorders	Uncommon	Hepatitis, jaundice, hepatic function abnormal
	Very rare:	Hepatic failure
Skin and Subcutaneous Tissue Disorders	Common	Rash
	Uncommon:	Urticaria, pruritus, purpura, angioedema
	Very rare:	Severe cutaneous adverse reactions (SCARs) (including, exfoliative dermatitis, Erythema multiforme, bullous reactions, including Stevens-Johnson syndrome, and toxic epidermal necrolysis)
	Not known	Fixed drug eruption Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), Acute generalised exanthematous pustulosis (AGEP), photosensitivity reaction
Immune System Disorders	Rare	Anaphylactic reaction
Investigations	Very rare	Decreased haemoglobin levels

Description of Selected Adverse Reactions

*Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

Toxicity

Signs and symptoms of toxicity have generally not been observed at doses below 100 mg/kg in children or adults. However, supportive care may be needed in some cases. Children have been observed to manifest signs and symptoms of toxicity after ingestion of 400 mg/kg or greater.

Symptoms

Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours.

The most frequently reported symptoms of overdose include nausea, vomiting, abdominal pain, lethargy and drowsiness. Central nervous system (CNS) effects include tinnitus, headache, dizziness, convulsion, and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnoea, diarrhoea and depression of the CNS and respiratory system have also been rarely reported.

Disorientation, excitation, fainting and cardiovascular toxicity, including hypotension, bradycardia and tachycardia have been reported. In cases of significant overdose, renal failure and liver damage are possible. Large overdoses are generally well tolerated when no other drugs are being taken. Exacerbation of asthma is possible in asthmatics.

Therapeutic measures

Patients should be treated symptomatically as required.

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam.

Give bronchodilators for asthma.

Other measures may be indicated by the patient's clinical condition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood glucose lowering drugs, Biguanide; ATC Code; A10B A02

Mechanism of action

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia or increased weight gain.

Its mode of action is multifactorial and not yet completely understood. However, the augmentation of glucose uptake into peripheral tissues may influence glucose utilisation.

Metformin may act via 3 mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
- and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

Pharmacodynamic effects

In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy

The prospective randomised study (UKPDS) has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes.

Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patient-years), $p=0.0023$, and versus the

combined sulfonylurea and insulin monotherapy groups (40.1 events/1000 patient-years), $p=0.0034$;

- a significant reduction of the absolute risk of diabetes-related mortality: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-years, $p=0.017$;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-years ($p=0.011$), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/1000 patient-years ($p=0.021$);
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1000 patient-years, diet alone 18 events/1000 patient-years ($p=0.01$).

Benefit regarding clinical outcome has not been shown for metformin used as second-line therapy, in combination with a sulfonylurea.

In type 1 diabetes, the combination of metformin and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

5.2 Pharmacokinetic properties

Absorption

After an oral dose of metformin hydrochloride tablet, maximum plasma concentration (C_{max}) is reached in approximately 2.5 hours (t_{max}). Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20- 30%.

After oral administration, metformin hydrochloride absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

At the recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin plasma levels (C_{max}) did not exceed 5 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following oral administration of a 850 mg tablet, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these findings is unknown.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately

the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63 and 276 litres.

Metabolism

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Characteristics in specific groups of patients

Renal impairment

The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations (see section 4.2).

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cores:

Pregelatinised starch

Maize starch

Maize starch as a 22% paste

Aerosil

Magnesium stearate
Coating:
Hypromellose
Macrogol 6000
Erythrosine lake FD&C Red no. 3 (E127)
Titanium dioxide (E171)
Dioctyl sodium sulphosuccinate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years when packed in tablets containers.

2 years when packed in blister packs.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container/outer carton

6.5 Nature and contents of container

Tablet container:

Pack sizes: 12, 21, 24, 28, 48, 56, 84, 96, 100, 250, 500 and 1000

Packaging composition: high density polyethylene.

Blister packs

Pack sizes: 12, 21, 24, 28, 48, 56 , 84, 96, 100

Packaging composition: rigid white PVC and 20 m aluminium foil.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

JCSH Pharma Ltd
Winslade, Shere Road, West Clandon, Surrey, GU4 8SF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 46447/0052

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

06/11/2024

10 DATE OF REVISION OF THE TEXT

17/12/2025