SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Impugan 10 mg/ml oral drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of Impugan oral drops contains 10 mg furosemide.

Excipient with known effect
Each ml contains 94 mg alcohol (ethanol); 9.4 % (w/V).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral drops, solution

Colourless or pale yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute pulmonary oedema. Cardiac, renal, hepatic and other forms of oedema. Hypertension.

4.2 Posology and method of administration

Posology

Adults
Oedema of different forms: 20-40 mg orally in the morning is usually enough. Sometimes higher doses are required, 80-160 (240) mg daily, preferably divided into 2-3 doses. Doses are increased gradually until satisfactory effect is obtained.
Hypertension: 20-80 mg daily. Impugan can be combined with other antihypertensive drugs, then the daily dose of each medicine may often be reduced.

Paediatric population
The suggested oral dose is 1-3 mg/kg of body weight.

Body weight	*Dose*	*Dosing interval*
<-5 kg	0.3-0.5 ml	1-3 times a day
5-10 kg	0.5-1.0 ml	1-3 times a day
10-15 kg	0.8-1.5 ml	1-3 times a day
15-20 kg	1.0-2.0 ml	1-3 times a day

Treatment control
Checks of plasma electrolytes should be performed regularly during long-term treatment, especially during simultaneous treatment with digitalis and at the beginning of the treatment.

Method of administration
The drops can be mixed with lukewarm tea or in cold milk. Acidic solutions such as fruit juices should be avoided.

4.3 Contraindications

Furosemide is contraindicated in:
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Patients who are allergic to sulphonamides
- Patients with hypovolaemia or dehydration
- Patients with precomatose or comatose conditions associated with hepatic encephalopathy.
- Patients with severe toxic renal damage (at high doses) and/or with anuric renal insufficiency

4.4 Special warnings and precautions for use

Symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with furosemide, particularly in the elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.

Furosemide should be administered with caution in premature infants (risk of development of nephrocalcinosis).

Severe sodium restricted diet should be avoided during treatment with diuretics.

Excipient(s)

Ethanol
The small amount of alcohol in this medicine will not have any noticeable effect.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per 24 ml, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations that should be avoided

Gentamicin
Concomitant i.v. administration of gentamicin (80 mg) and furosemide (40 mg) decreases the clearance of gentamicin with approximately 40%, with elevated plasma concentrations as a result. Simultaneous administration of these medicines should be avoided.

Furosemide may intensify the ototoxicity of aminoglycosides and other ototoxic drugs.

Combinations that may require dose adjustment

Digitalis glycosides
Induced hypokalemia may enhance digitalis effect (intoxication risk).

Sotalol
Hypokalemia associated with thiazide therapy is believed to increase the risk of arrhythmias triggered by sotalol (syncope, prolonged QT).

Nonsteroidal anti-inflammatory/antirheumatic agents, NSAIDs
Antiphlogistics of NSAID-type (indomethacin, propionic acid) have been shown to counteract the diuretic effect of furosemide and bumetanide, possibly via inhibition of prostaglandin synthesis. They can also counteract the antihypertensive effect of thiazides. This interaction is not likely to occur with sulindac and is possibly insignificant for selective COX-2 inhibitors. In patients with dehydration or hypovolaemia, non-steroidal anti-inflammatory drugs may cause acute renal insufficiency.

Lithium

Thiazides reduce renal excretion of lithium, which can result in increased plasma concentrations with unchanged lithium dosages. A recent study suggests that loop diuretics (furosemide) have little such effect.

ACE inhibitors
Studies on patients with chronic heart failure show that captopril (and probably other ACE inhibitors) reduces the diuretic and natriuretic effect of furosemide. Patients receiving diuretic therapy may develop severe hypotension and impaired renal function when an ACE inhibitor is used for the first time or is first used in a higher dose ("first-dose hypotension").

Aliskiren
Aliskiren reduces the plasma concentration of orally administered furosemide. It is recommended to monitor the diuretic effect of furosemide when starting and adjusting the dose of concomitant treatment with aliskiren.

Other interactions
The antihypertensive effect increases when combined with specific antihypertensive drugs. Concomitant administration of furosemide, in high doses, and cephalothin/cephaloridine has occasionally been reported to enhance the nephrotoxic effect of cephalothin/cephaloridine. In patients with high salicylate intake, furosemide can cause salicylate toxicity by inhibiting renal salicylate excretion.

4.6 Fertility, pregnancy and lactation

Pregnancy
Generally furosemide should only be used for specific indications during pregnancy.

Thiazides, thiazide diuretics and loop diuretics may pass to the fetus and cause electrolyte imbalance. Cases of neonatal thrombocytopenia have been described with thiazide and thiazide-diuretics. This risk probably excists with the use of loop diuretics such as furosemide and bumetanide. During the last trimester Impugan should only be given after careful consideration and in the lowest appropiate dose.

Breastfeeding
Furosemide passes into breast milk in quantities that may affect the child even in therapeutic doses. Diuretics inhibit lactation and are therefore unsuitable for breastfeeding women.

4.7 Effects on ability to drive and use machines

Impugan has minor or insignificant influence on the ability to drive and use machines.

4.8 Undesirable effects

Most side effects are dose dependent. The most common are disturbance of electrolyte and fluid balance (about 5%), which are associated with the physiological effect that primarily occurs in patients with impaired hepatic function and in patients with renal insufficiency that take high doses .

BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Uncommon (≥1/1,000 to <1/100)	Aplastic anaemia
Rare (≥1/10,000 to <1/1,000)	Leukopaenia, agranulocytosis, thrombocytopaenia
METABOLISM AND NUTRITION DISORDERS	
Common (≥1/100 to <1/10)	

Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	Hypomagnesaemia, hypokalaemia, hyperuricaemia, hypochloraemia, hyponatraemia, hypocalcaemia Dehydration Hyperglycaemia
NERVOUS SYSTEM DISORDERS Not known (cannot be estimated from the available data)	 Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension)
EAR AND LABYRINTH DISORDERS Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	 Deafness (sometimes irreversible) Tinnitus and reversible deafness (in high plasma concentrations)
VASCULAR DISORDERS Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	 Hypovolaemia in intensive therapy Hypotension Vasculitis
GASTROINTESTINAL DISORDERS Uncommon (≥1/1,000 to <1/100) Not known (cannot be estimated from the available data)	 Nausea, vomiting Acute pancreatitis
HEPATOBILIARY DISORDERS Rare (≥1/10,000 to <1/1,000) Not known (cannot be estimated from the available data)	 Hepatic reactions such as elevated hepatic enzymes Intrahepatic cholestasis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS Rare (≥1/10,000 to <1/1,000) Not known (cannot be estimated from the available data)	 Rash, pruritus, urticaria, exfoliative dermatitis, erythema multiforme, purpura, , Stevens-Johnsons syndrome, toxic epidermal necrolysis, photosensitization Acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS)
RENAL AND URINARY DISORDERS Very common (≥1/10)	 Nephrocalcinosis in infants

Not known (cannot be estimated from the available data)	Interstitial nephritis, worsening of renal dysfunction

The serum electrolytes are usually within normal ranges at doses lower than typically used in treatment of e.g. cardiac and renal oedema.

Hypokalemia, possibly with hypochloremic alkalosis may occur particularly at forced diuresis, caution should be taken during concomtant use with digitalis.

Hypovolemia may occur at high oral doses. At serum concentrations higher than 50 µg/ ml hearing loss has been reported. This is usually reversible.

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 national reporting system listed in Appendix V.

4.9 Overdose

Toxicity: 80 mg in 1-2 year olds gave mild intoxication, and 240-320 mg in a 2 year old gave moderate intoxication. 600-800 mg in a 14 year old gave moderate intoxication, 420-500 mg in the elderly caused mild to moderate intoxication.

Symptoms: Disturbance of electrolyte and fluid balance, thirst, dehydration, metabolic alkalos. Initial polyuria, with big losses of fluids oliguria, anuria. Following fluid and electrolyte losses, headache, confusion, dizziness, paresthesias, muscle weakness, possible. Convulsions and coma, orthostatic hypotension, syncope, ECG changes, arrhythmias. Nausea, vomiting, abdominal pain.

Treatment: Gastric lavage if needed, activated charcoal. Rehydration adjustment of electrolyte and acid-base balance. Continuous ECG- monitoring for severe dehydration/electrolytedisturbance. Other symptomatic therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: High-ceiling diuretics, ATC code: C03CA01

Furosemide is a sulfonamide derivative and a "high-ceiling" diuretic which means a dose-dependent effect over a wide dose range. The effect has a rapid onset and short duration. Furosemide acts primarily through inhibition of chloride reabsorption in the ascending limb of Henle's loop, but also exerts an effect in the proximal and distal tubules. In parallel with the increased chloride excretion, the excretion of sodium, calcium, potassium and magnesium is increased. Also potassium excretion increases, while excretion of bicarbonate is practically unaffected. The resulting diuresis is strong with a subsequent, usually mild, blood pressure lowering effect. In pulmonary oedema, furosemide induces a rapid increase in venous capacity before the onset of diuresis, bringing about a decrease in the filling pressure in the left chamber.

Furosemide has also, usually mild, antihypertensive effect that sets in later and lasts longer than the diuretic effect.

Since the blood pressure lowering effect with loop diuretics is milder than with thiazides, loop diuretics should only be used for hypertension treatment to potentiate other drugs, by increasing the

diuresis. Indication for loop diuretics is primarily when renal function is impaired. A normal blood pressure is not affected or only slightly affected.

5.2 Pharmacokinetic properties

Furosemide is absorbed rapidly from the gastrointestinal tract. Peak serum concentrations are normally reached after ½-2 hours after oral administration. The absorption of furosemide may be delayed and reduced with concomitant food intake. In the case of severe oedema, reduced bioavailability has been reported, probably due to reduced absorption from the gastrointestinal tract. The diuretic effect normally sets in after ½-1 hour and reaches maximum after 1-2 hours. It lasts 4-6 hours. Protein binding has been estimated to be 91-99%. The half-life is normally 1-2 hours and longer in infants as well as in patients with liver and kidney disease. The main part is excreted within 10 hours after a dose. 24 hours after a single dose there are no measurable amounts of furosemide in the urin. 2/3 of furosemide is excreted unchanged by glomerular filtration and tubular secretion and the remainder via faeces.

5.3 Preclinical safety data

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium saccharin
Sodium hydroxide
Ethanol 96 % (V/V)
Water for injections

6.2 Incompatibilities

The droplets are miscible in neutral solutions. This medicinal product must not be mixed with acidic solutions.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Bottle with graduated dose pipette, 30 ml

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2024-07-12