PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

ASCEPRIB IV 400 solution for infusion

ASCEPRIB IV 600 solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ASCEPRIB IV 400: Each 100 ml contains 400 mg of ibuprofen

ASCEPRIB IV 600: Each 100 ml contains 600 mg of ibuprofen

Sugar free

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for infusion

Clear and colourless to pale yellow solution for infusion, free of visible particles.

pH: 6,5 to 7,8

Osmolality: 310 to 360 mOsm/l

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ASCEPRIB IV is indicated for the short-term treatment of mild to moderate pain of inflammatory origin and fever when oral administration is inappropriate.

4.2 Posology and method of administration

Posology

Use the lowest effective dose for the shortest possible duration of treatment (see section 4.4).

Use should be limited to situations where oral administration is inappropriate. Patients must switch to oral treatment as soon as this is possible.

ASCEPRIB IV is indicated for short-term acute treatment only and should not be used for more than 3 days.

Adequate hydration of the patient should be maintained to minimize the risk of possible renal adverse reactions.

Adults

One dose of 400 mg or 600 mg of ibuprofen. If clinically justified, another dose can be administered after 6 to 8 hours depending on the intensity of the treatment. The maximum total daily dose is 1 200 mg.

Special populations

Elderly patients

Precautions should be taken when treating elderly patients as they are generally more prone to adverse effects (see section 4.4 and 4.8), and are more likely to have renal, hepatic and cardiovascular dysfunction and to be using concomitant medications. Specifically, it is recommended to administer the lowest effective dose for the shortest duration necessary to control symptoms for this population. Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Renal insufficiency

Precautions should be taken when NSAIDs are used in patients with renal insufficiency. In patients with mild or moderate renal impairment the initial dose

should be reduced and be kept as low as possible for the shortest duration necessary to control symptoms and renal function should be monitored. ASCEPRIB IV is contraindicated in patients with severe renal insufficiency (see section 4.3).

Hepatic insufficiency

Precautions should be taken when NSAIDs are used in this population although differences in the pharmacokinetic profile have not been observed. Patients with mild or moderate hepatic insufficiency should start the treatment with reduced doses, the dose should be kept as low as possible for the shortest duration necessary and they should be carefully monitored. ASCEPRIB IV is contraindicated in patients with severe hepatic insufficiency (see section 4.3).

Paediatric population

ASCEPRIB IV should not be used in children and adolescents. The use of ASCEPRIB IV has not been studied in children and adolescents. Therefore, the safety and efficacy have not been established.

Method of administration

For intravenous use. Restricted to hospital use only.

The solution should be administered as an intravenous infusion over 30 minutes.

4.3 Contraindications

- Hypersensitivity to ibuprofen or to any of the excipients (see section 6.1)
- Heart failure
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including ASCEPRIB IV.

- Active or history of recurrent ulcer/haemorrhage/perforations.
- Pregnancy (see section 4.6).
- Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria), in response to ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs.
- Renal failure.
- Conditions involving an increased tendency or active bleeding such as thrombocytopenia.
- Severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).
- Children and adolescents (see section 4.2).

4.4 Special warnings and precautions for use

Cardiovascular events

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with ASCEPRIB IV therapy. In view of the ASCEPRIB IV's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Caution is required in patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) and should only be treated with ASCEPRIB IV after careful consideration.

Elderly

The elderly has an increased frequency of adverse reactions to NSAIDs including ASCEPRIB IV, especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.

Gastrointestinal

The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with

increasing doses of ASCEPRIB IV, in patients with a history of ulcers, and the elderly.

When gastrointestinal bleeding or ulceration occurs in patients receiving ASCEPRIB IV, treatment with ASCEPRIB IV should be stopped.

ASCEPRIB IV should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

Dermatological

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. ASCEPRIB IV should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity (see section 4.8).

Pregnancy

Regular use of NSAIDs such as ASCEPRIB IV during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed, and its duration increased.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients receiving NSAIDs such as ASCEPRIB IV. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this

disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue ASCEPRIB IV and evaluate the patient immediately.

Respiratory

Bronchospasm may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease.

Anaphylactoid reactions

As standard practice during intravenous infusion, close patient monitoring is recommended, especially at the beginning of the infusion to detect any anaphylactic reaction caused by the active substance or the excipients.

Severe acute hypersensitivity reactions (e.g. anaphylactic shock) are rarely observed. At the first signs of a hypersensitivity reaction following the administration of ibuprofen, therapy must be stopped, and symptomatic treatment must be established. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

Ibuprofen 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. Some cases of aseptic meningitis have been reported with the use of ibuprofen in patients with systemic lupus erythematosus (SLE). Aseptic meningitis is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases.

Precautions regarding excipients

ASCEPRIB IV 400 contains 15,56 mmol (358 mg) sodium per bottle.

ASCEPRIB IV 600 contains 15,65 mmol (360 mg) sodium per bottle.

To be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

NSAIDs

Use of two or more NSAIDs concomitantly could result in an increase in side effects.

Corticosteroids

Increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).

Anti-coagulants

ASCEPRIB IV may enhance the effects of anti-coagulants such as warfarin.

Anti-platelet and selective serotonin reuptake inhibitors (SSRIs)

Anti-platelet medicines (e.g. clopidogrel and tioclopidine) and SSRIs can cause an increased risk of gastrointestinal bleeding.

Anti-hypertensive, beta-blockers and diuretics

ASCEPRIB IV may reduce the effect of anti-hypertensives, such as ACE inhibitors, beta-blockers and diuretics.

Diuretics can also increase the risk of nephrotoxicity of ASCEPRIB IV.

Cardiac glycosides

ASCEPRIB IV may exacerbate cardiac failure, reduce GFR and increase plasma glycoside (e.g. digoxin) levels.

Lithium

Decreased elimination of lithium and potentially increase plasma levels of lithium.

Ciclosporin

Increased risk of nephrotoxicity.

Mifepristone

A decrease in the efficacy of the medicine can occur due to the anti-prostaglandin properties of ASCEPRIB IV. ASCEPRIB IV should not be used for 8-12 days after mifepristone administration.

Quinolone antibiotics

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

Aminoglycosides

ASCEPRIB IV may decrease the excretion of aminoglycosides.

Herbal extracts

Ginkgo biloba may potentiate the risk of bleeding with ASCEPRIB IV.

Methotrexate

There may be potential increases in plasma methotrexate concentration in renal dysfunction.

Tacrolimus

Possible increased risk of nephrotoxicity when ASCEPRIB IV is given with tacrolimus.

Zidovudine

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

4.6 Fertility, pregnancy and lactation

Pregnancy

ASCEPRIB IV is contraindicated in pregnancy (see section 4.3)

First trimester

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about 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 %. 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.

Second and third trimester.

During the third trimester of pregnancy, prostaglandin synthesis inhibitors, may expose the foetus to: cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension); renal dysfunction, which may progress to renal failure with oligo-hydroamniosis.

At the end of pregnancy, the mother and the neonate may be exposed 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.

Breastfeeding

In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breastfed infant adversely.

Fertility

Females

Based on the mechanism of action, the use of prostaglandin mediated NSAIDs,

including ASCEPRIB IV, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Consider withdrawal of ASCEPRIB IV in women who have difficulties conceiving or who are undergoing investigation of infertility.

4.7 Effects on ability to drive and use machines

Undesirable effects such as nausea, dizziness, drowsiness, fatigue and visual disturbances are possible after taking ASCEPRIB IV (see section 4.8). If affected, patients should be advised not to drive or operate machinery.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforations or gastrointestinal bleeding, sometimes fatal.

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Less frequent	Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis)
Blood and lymphatic system disorders	Less frequent	Haematopoietic disorders (anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial

MedDRA system organ class	**Frequency**	**Adverse reactions**
		mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising
Immune system disorders	Less frequent	Hypersensitivity reactions with urticaria and pruritus, severe hypersensitivity reactions. Symptoms could be facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).
	Frequency unknown	In patients with existing autoimmune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed. Respiratory tract reactivity, e.g. asthma, aggravated asthma, bronchospasm, dyspnoea.

MedDRA system organ class	**Frequency**	**Adverse reactions**
		Exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme)
Psychiatric disorders	Less frequent	Anxiety, restlessness, psychotic reactions, nervousness, confusion or disorientation and depression
Nervous system disorders	Frequent	Fatigue, insomnia, headache, dizziness
	Less frequent	Agitation, irritability
Eye disorders	Less frequent	Visual disturbances, reversible toxic amblyopia
Ear and labyrinth disorders	Frequent	Vertigo
	Less frequent	Tinnitus, hearing disorders
Cardiac disorders	Less frequent	Palpitations, oedema, hypertension, cardiac failure, myocardial infarction
Vascular disorders	Less frequent	Arterial hypertension
Respiratory, thoracic and mediastinal disorders	Less frequent	Asthma, bronchospasm, dyspnoea and wheezing
Gastrointestinal disorders	Frequent	Pyrosis, abdominal pain, nausea, vomiting, flatulence, diarrhoea,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		constipation, peptic ulcers, perforations or gastrointestinal bleeding, sometimes fatal, ulcerative stomatitis, gastritis, exacerbation of colitis and Crohn's disease
	Less frequent	Dyspepsia, melaena, gastritis, oesophageal stenosis, exacerbation of diverticular disease, unspecific haemorrhagic colitis, oesophagitis, pancreatitis
Hepato-biliary disorders	Less frequent	Jaundice, hepatic dysfunction, hepatic damage (particularly in long-term therapy), acute hepatitis
	Frequency unknown	Hepatic insufficiency
Skin and subcutaneous tissue disorders	Frequent	Skin eruption
	Less frequent	Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, photosensitivity reactions
	Frequency	Drug reaction with eosinophilia

MedDRA system organ class	**Frequency**	**Adverse reactions**
	unknown	and systemic symptoms (DRESS syndrome)
Musculoskeletal and connective tissue disorders	Less frequent	Stiff neck
Renal and urinary disorders	Less frequent	Reduced urinary excretion, particularly in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nephritis, acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.
General disorders and administration site conditions	Frequent	Pain and burning sensation in the administration site
	Frequency unknown	Site of injection reactions such as swelling, haematoma or bleeding

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**",

found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

Central nervous system disturbances include headache, tinnitus, nausea, dizziness, light-headedness, unconsciousness and ataxia, as well as abdominal pain, nausea and vomiting, may occur as symptoms of an overdose. In addition, gastrointestinal bleeding, as well as functional disturbances of the liver and kidneys, is possible. There may furthermore be hypotension, respiratory depression and cyanosis.

Treatment

Treatment is symptomatic and there is no specific antidote. If recently taken, gastric lavage will remove any unabsorbed ibuprofen. Electrolytes may be corrected by intravenous infusions, if necessary. Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 3.1 Anti-rheumatics (anti-inflammatory agents)

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, non-steroids.

ATC code: M01AE01

Chemically, ibuprofen is described as 2-(4-isobutylphenyl) propionic acid and is a

non-steroidal compound, which exhibits anti-inflammatory, analgesic and anti-pyretic activities.

Furthermore, ibuprofen reversibly inhibits ADP- and collagen-induced platelet aggregation.

5.2 Pharmacokinetic properties

Absorption

After intravenous administration of ibuprofen in humans, the maximum concentration (C_{max}) of S-enantiomer (active) and R-enantiomer is reached at approximately 40 minutes, with a rate of infusion of 30 minutes.

Distribution

The estimated volume of distribution is 0,11 to 0,21 l/kg. Ibuprofen is extensively bound to plasma proteins, primarily albumin.

Biotransformation

Ibuprofen is metabolised in the liver into two inactive metabolites, and these together with unmetabolised ibuprofen, are excreted by the kidney either as such or as conjugates.

After on oral application, ibuprofen is already partly absorbed in the stomach and then completely in the small intestine. Following hepatic metabolisation (hydroxylation, carboxylation), the pharmacologically inactive metabolites are completely eliminated, mainly renally (90 %), but also with the bile.

Elimination

Excretion by the kidney is rapid and complete. The elimination half-life is about 2

hours.

Linearity/non-linearity

Ibuprofen shows linearity in the area under the curve of plasma concentration time after a single administration of ibuprofen (in a range of 200 to 800 mg).

Pharmacokinetic/pharmacodynamic relationship (s)

There is a correlation between plasma levels of ibuprofen, its pharmacodynamic properties and overall safety profile. Ibuprofen pharmacokinetics is stereo-selective after intravenous and oral administration. The mechanism of action and pharmacology of intravenous ibuprofen do not differ from mechanism of oral ibuprofen.

Special populations

Renal impairment

For patients with mild renal impairment; increased unbound (S)-ibuprofen, higher AUC values for (S)-ibuprofen and increased enantiomeric AUC (S/R) ratios have been reported compared with healthy controls.

In end-stage renal disease patients receiving dialysis the mean free fraction of ibuprofen was about 3 % compared with about 1 % in healthy volunteers.

Severe impairment of renal function may result in accumulation of ibuprofen metabolites. The significance of this effect is unknown. The metabolites can be removed by haemodialysis (see sections 4.3).

Hepatic impairment

In cirrhotic patients with moderate hepatic impairment (Child Pugh's score 6-10) treated with racemic ibuprofen an average 2-fold prolongation of the half-life was

observed and the enantiomeric AUC ratio (S/R) was significantly lower compared to healthy controls, suggesting an impairment of metabolic inversion of (R)-ibuprofen to the active (S)-enantiomer (see sections 4.3).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine

Sodium chloride

Hydrochloric acid (for pH adjustment) E507

Sodium hydroxide (for pH adjustment) E524

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, ASCEPRIB IV must not be mixed with other products.

6.3 Shelf life

4 years (48 months) for Asceprib IV 600

6.4 Special precautions for storage

No special storage conditions required.

6.5 Nature and contents of container

100 ml LDPE container with Twincap.

10 or 20 bottles are packed in an outer cardboard box.

6.6 Special precautions for disposal and other handling

ASCEPRIB IV is indicated for use as single dose; any unused solution should be discarded. Before administration, the solution should be visually inspected to ensure it is clear and colourless. It should not be used if any particulate matter is observed.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ascendis Pharma (Pty) Ltd.

31 Georgian Crescent East

Bryanston

2191

8 REGISTRATION NUMBERS

ASCEPRIB IV 400: 53/3.1/0017

ASCEPRIB IV 600: 53/3.1/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 June 2023

10 DATE OF REVISION OF THE TEXT