SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[SE:]
Paracetamol/Phenylephrine Navamedic 500 mg/10 mg powder for oral solution

[NO:]
Paracetamol/Phenylephrine Navamedic 500 mg/12,2 mg powder for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains:

Paracetamol	500 mg
Phenylephrine hydrochloride	12,2 mg corresponding to phenylephrine 10,0 mg

Excipients with known effect
Each sachet contains sucrose 1,8 g, aspartame (E951) 17,5 mg, sorbitol (E420) 1 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for oral solution
Single-dose sachet containing a free flowing white powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paracetamol/Phenylephrine Navamedic is indicated for short term symptomatic treatment of colds and influenza (aches, fever) when associated with nasal congestion,in adults and children over 16 years of age.

4.2 Posology and method of administration

Posology

Adults
One sachet dissolved by stirring in hot water (125 ml).
The dose may be repeated in 4-6 hours.
No more than four doses should be taken in 24 hours.

Children under 16 years of age
Paracetamol/Phenylephrine Navamedic is not recommended for use in children below the age of 16 years without medical advice.

Children over 16 years of age
One sachet dissolved by stirring in hot water (125 ml).
The dose may be repeated in 4-6 hours.
No more than four doses should be taken in 24 hours.

Elderly

There is no indication that dosage needs to be modified in the elderly.

Method of Administration
Oral administration after dissolution in water.

4.3 Contraindications

- Hypersensitivity to the active substances paracetamol or phenylephrine or to any of the excipients listed in section 6.1.
- Severe coronary heart disease
- Hypertension
- Glaucoma
- Hyperthyroidism
- Use in patients taking tricyclic antidepressants
- Use in patients who are currently taking or have taken monoamine oxidase inhibitors (MAOIs) within the last 2 weeks
- Severe impairment of liver function
- Acute Hepatitis
- Alcohol abuse

4.4 Special warnings and precautions for use

Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as renal impairment and sepsis, or in patients with malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Use with caution in patients with
- Raynaud's phenomenon
- Diabetes
- Moderate and severe renal insufficiency
- Liver function disorders:
  mild to moderate hepatocellular insufficiency (including Gilbert’s syndrome), concomitant treatment with medicinal products affecting hepatic functions
- haemolytic anaemia,
- dehydration
- chronic malnutrition
- glutathione depletion due to metabolic deficiencies

This product should not be combined with other medicinal products that contain paracetamol. Higher doses than recommended may lead to severe liver damage. Clinical signs of liver damage normally become evident 2 days after ingestion. Antidote should be given as soon as possible. See also section 4.9.

This medicine contains sucrose
Contains 1,8 g sucrose per sachet. This should be taken into account in patients with diabetes mellitus.Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains sorbitol
Contains 1 mg sorbitol (E420) per sachet.

This medicine contains aspartame
Contains 17,5 mg aspartame (E951) each sachet. Aspartame is a source of phenylalanine. It may be harmful for people with phenylketonuria, a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

This medicine is essentially 'sodium-free'
Contains less than 1 mmol sodium (23 mg) per sachet, that is to say essentially 'sodium-free'.

Medical supervision is recommended if symptoms are not relieved or deteriorate within 3 days of therapy with Paracetamol/Phenylephrine Navamedic.

Aspirin-hypersensitive asthmatics may also be hypersensitive to Paracetamol/PhenylephrineNavamedic.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol
Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).
Drugs which induce hepatic microsomal enzymes, such as alcohol, barbiturates, anticonvulsants such as phenytoin, phenobarbital, methylphenobarbital and primidone, rifampicin, monoamine oxidase inhibitors and tricyclic antidepressants, may increase the hepatotoxicity of paracetamol, particularly after overdosage.
The speed of absorption of paracetamol may be decreased by anticholinergic drugs (e.g., glycopyrronium, propantheline), and increased by metoclopramide or domperidone and absorption reduced by cholestyramine. Isoniazide reduces paracetamol clearance with possible potentiation of its action and/or toxicity, by inhibition of its metabolism in the liver. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect. Probenecid reduces clearance of paracetamol by inhibiting conjugation with glucoronic acid.
Regular use of paracetamol possibly reduces metabolism of zidovudine (increased risk of neutropenia).

Phenylephrine
Phenylephrine may adversely interact with other sympathomimetics, vasodilators and beta-blockers and other antihypertensives.
The vasopressor effects of phenylephrine can be potentiated by digoxin, MAO inhibitors, tricyclic antidepressants such as amitriptyline, amoxapine, clomipramine, desipramine and doxepine or tetracyclics such as maprotiline; antidepressants such as phenelzine, isocarboxylic acid, nialamide, tranylcipromine, moclobemide; Parkinson's disease drugs such as selegiline, and others such as furazolidone.
Contraindicated for patients currently receiving or within two weeks of stopping therapy with monoamine oxidase inhibitors

Paediatric population
Frequency, type and severity of interactions in children over the age of 16 years are expected to be the same as in adult.

4.6 Fertility, pregnancy and lactation

Fertility
There is no evidence from non-clinical studies indicating effects of paracetamol on male or female fertility at clinically relevant doses. The effects of phenylephrine on male or female fertility have not been studied.

Pregnancy
Paracetamol
A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.
Phenylephrine
There are limited data on the use of phenylephrine in pregnant women. Vasoconstriction of uterine vessels and reduced uterine blood flow associated with use of phenylephrine may result in fetal hypoxia. Until more information is available, use of phenylephrine should be avoided during pregnancy.

Breastfeeding
Paracetamol
Paracetamol is excreted in breastmilk, but not in a clinically significant amount. Available published data do not contraindicate breast feeding.
Phenylephrine
There are no data available on whether phenylephrine is released into breast milk and no reports on the effects of phenylephrine on the nursing infant. Until more data are available, use of phenylephrine should be avoided in lactating woman.

In summary Paracetamol/Phenylephrine Navamedic is not recommended during pregnancy and lactation

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No such effects have been described to date.

4.8 Undesirable effects

The frequency of occurrence of undesirable effect is usually classified as follows
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), not known (cannot be estimated from the available data)

Paracetamol

System organ class	**Rare (≥1/10 000 to <1/1 000)**	**Very rare (<1/10 000)**	**not known (cannot be estimated from the available data)**
Blood and lymphatic system disorders	Blood dyscrasias including platelet disorders, agranulocytosis, leucopenia, thrombocytopenia, haemolytic anaemia, pancytopenia		Anaemia

Immune system disorders	Allergic or hypersensitivity reactions including skin rashes, urticaria, anaphylaxis and bronchospasm		Anaphylactic shock
Metabolism and nutrition disorders			High anion gap metabolic acidosis
Nervous system disorders			Vertigo
Respiratory, thoracic and mediastinal disorders			Oedema of the larynx
Gastrointestinal disorders		Acute pancreatitis	Gastro intestinal effects
Hepatobiliary disorders	Abnormal hepatic function (increase in hepatic transaminases), hepatic failure, hepatic necrosis, jaundice.		Liver alteration and hepatitis
Skin and subcutaneous tissue disorders	Hypersensitivity including skin rash and urticaria, pruritus, sweating, purpura, angioedema	Serious skin reactions (Drug induced Stevens-Johnson syndrome-SJS, toxic epidermal necrolysis-TEN, and acute generalised exanthematous pustulosis-AGEP)	Erythema multiforme , , , , and
Renal and urinary disorders		Interstitial nephritis after prolonged use of high doses of paracetamol Sterile pyuria (cloudy urine)	Renal alteration (severe renal impairment, haematuria, anuresis)

Description of selected adverse reactions

<u>High anion gap metabolic acidosis</u>
Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

<u>Paediatric population</u>
Frequency, type and severity of adverse reactions in children over the age of 16 years are expected to be the same as in adults.

Phenylephrine

System organ class	Common (≥1/100 to <1/10)	Rare (≥1/10 000 to <1/1 000)	Very rare (<1/10 000)	not known (cannot be estimated from the available data)
Immune system disorders		Allergic or hypersensitivity reactions including skin rash, urticaria, anaphylaxis and bronchospasm		
Nervous system disorders			Insomnia, nervousness, tremor, anxiety, restlessness, confusion, irritability, dizziness and headache may occur	
Cardiac disorders		Tachycardia, palpitation		
Vascular disorders		Blood pressure increase		
Gastrointestinal disorders	Anorexia, nausea and vomiting			

Information about population > 16 years of age
Frequency, type and severity of adverse reactions in children over the age of 16 years are expected to be the same as in adults.

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

Liver damage is possible in adults who have taken a single dose of 10 g or more of paracetamol. Ingestion of a single dose of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors (see below).

Risk Factors
If the patient:
- Is on long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. John's Wort or other drugs that induce liver enzymes, or
- Regularly consumes ethanol in excess of recommended amounts, or

- Is likely to be glutathione deplete, e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia, or
- is a young child, or
- has a liver disease.

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. 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.

After prolonged use of high doses of paracetamol hypokalemia may develop.

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. Management of patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be discussed with the specialised services or a liver unit.

Hypertensive effects may be treated with an i.v. alpha-receptor blocking agent.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: paracetamol combinations excl. psycholeptics,ATC- Code: N02BE51

Mechanism of action Paracetamol
In vivo, paracetamol has both analgesic and antipyretic activity, which is believed to be mediated through inhibition of the cyclooxygenase (COX) pathway within the central nervous system. Although this mechanism is shared with the nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol does not have significant anti-inflammatory activity nor does it inhibit production of pro-clotting thromboxanes. Additional pathways such as the serotonergic descending pain pathways may be involved in the antinociceptive effect of paracetamol.

Mechanism of action Phenylephrine
Phenylephrine is a potent alpha1-adrenoceptor agonist. Its action on the peripheral $alpha_1$ receptors induces vasoconstriction, which in the nasal mucosa, reduces oedema and nasal swelling. When given intravenously, phenylephrine consistently increases total peripheral resistance (TPR), systolic (SBP)

and diastolic (DBP) blood pressure, while heart rate declines as a result of reflex bradycardia. The hemodynamic alterations brought about by IV phenylephrine may differ according to age and baseline blood pressure. Young normotensive subjects will show larger heart rate decreases and lower SBP increases than young hypertensives and old normotensives, while old hypertensives show the least pronounced reflex bradycardia and most pronounced SBP rise. The orally administered drug has not demonstrated consistent cardiovascular effects at the recommended doses of 10 – 12.2 mg QID, and oral doses of 40 to 60 mg are needed to elicit clinically meaningful cardiovascular effects such as increased diastolic blood pressure and reflex cardiac slowing.

Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and monoamine oxidase inhibitors. Phenylephrine may reduce the efficacy of beta-blocking drugs and antihypertensive drugs.

5.2 Pharmacokinetic properties

Paracetamol
Absorption/Distribution
The absolute bioavailability of orally administered paracetamol is 75 %, and is probably subject to first-pass metabolism. Tmax, though formulation-dependent, is usually between 30 and 120 minutes. The extent of absorption is however not formulation-dependent.

Elimination
Half-life is approximately 2 - 2.5 hours.

Biotransformation
The major metabolites are glucuronide and sulphate conjugates (>80 %) which are excreted in urine. A small amount (<10 %) of paracetamol is oxidized in the liver by cytochrome P4502E1 (CYP2E1). This reaction produces the highly reactive metabolite N-acetyl- p-benzoquinone imine (NAPQI), which is responsible for the characteristic centrilobular hepatotoxicity associated with paracetamol overdoses.

Phenylephrine
Absorption/Distribution
When administered by intravenous infusion, free 3H-phenylephrine concentration peaks at the end of the infusion, after serum concentration declines in a biexponential pattern, with an 80 % decline in the first 15 minutes, followed by a slower decline with an average half-life of 2 hours. When taken orally, phenylephrine is absorbed from the gastrointestinal tract with a serum peak between 45 and 75 minutes.

Elimination
Following a short phase of fast elimination, the average elimination half-life is 2.5 hours. At steady state, the volume of distribution is 340 l, indicating storage in certain organ compartments. Renal clearance is only a fraction of total plasma clearance.

Biotransformation
Due to extensive first-pass metabolism, total phenylephrine bioavailability is approximately 38 %, of which 1% is active, non-conjugated parent phenylephrine.

Phenylephrine retains activity as a nasal decongestant when given orally, the drug distributing through the systemic circulation to the vascular bed of nasal mucosa. When taken by mouth as a nasal decongestant phenylephrine is usually given at intervals of 4-6 hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Paracetamol
Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ascorbic acid,
sucrose,
aspartame (E951),
lemon flavours (containing: natural lemon oils and natural and nature identical flavouring substances, maltodextrin, mannitol (E 421), gluconolactone, acacia gum, sorbitol (Ph.Eur.) (E420), silica colloidal anhydrous and all-rac-α-tocopherol (E 307)),
saccharin sodium,
silica colloidal anhydrous,
citric acid,
sodium citrate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

Duration of storage after reconstitution:
The reconstituted solution in hot water is stable for 60 min at room temperature.

6.4 Special precautions for storage

Store in the original container in order to protect from light and moisture.
For storage conditions after reconstitution of the medicinal product, see section 6.3

6.5 Nature and contents of container

The sachet foil is composed of paper, glue or polyethylene, aluminium and sealing layer.
6, 8, 10, 12, 16, 20, 24, 32, 36, 40 sachets are contained in a cardboard carton.
10, 20 sachets are contained in a cardboard carton.

Not all pack sizes may be marketed

6.6 Special precautions for disposal <and other handling>

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Navamedic ASA
Postbox 2044 Vika
0125 Oslo
Norway

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

3-Apr-2025