SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

ParaCo-Denk 1000/60 Suppositories

2. Qualitative and quantitative composition

Active substances: paracetamol, codeine
Each suppository contains 1,000 mg paracetamol and 60 mg codeine phosphate hemihydrate (equivalent to 44.2 mg codeine).

Excipient with known effect: soya lecithin.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Suppository
White to ivory coloured, torpedo shaped suppositories.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ParaCo-Denk is indicated in children aged 12 years and older, adolescents and adults for the treatment of moderate to severe pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

4.2 Posology and method of administration

Posology
Posology with single and daily doses: Children aged 12 years and older, adolescents and adults should use 1 suppository, up to 4 times a day if required.
Paracetamol is dosed by body weight and age (usually 10 to 15 mg/kg body weight as a single dose). With reference to the paracetamol portion of the fixed combination, the total daily dose must not exceed 60 mg/kg body weight.
With reference to the codeine portion of the fixed combination, this gives a maximum daily dose of 240 mg codeine phosphate hemihydrate (equivalent to 4 suppositories).

The corresponding dosage interval is based on the symptoms and the maximum total daily dose. It should be not less than 6 hours.

Body weight (Age)	**Single dose** (equivalent paracetamol and codeine phosphate hemihydrate dose)	**Max. daily dose (24 hrs)** (equivalent paracetamol and codeine phosphate hemihydrate dose)
43 kg and over (children ≥ 12 years, adolescents and adults)	**1 suppository** (equivalent to 1,000 mg paracetamol and 60 mg codeine phosphate hemihydrate)	**4 suppositories** (equivalent to 4,000 mg paracetamol and 240 mg codeine phosphate hemihydrate)

The maximum daily dose (24 hours) stated in the table must not be exceeded under any circumstances.

Special populations

Liver insufficiency and mild kidney failure:
In patients with impaired hepatic or renal function or with Gilbert's syndrome, dosage must be reduced or the dosage interval extended. Unless otherwise indicated by a doctor, a daily dose of 2 g paracetamol should not be exceeded.

Severe kidney failure
This product is not suitable for patients with kidney failure if a reduced dose is required. Suitable pharmaceutical forms are available.

Elderly patients
No dose adjustment is required.

Paediatric population
Paracetamol/codeine suppositories (1000 mg/60 mg) are not recommended in children below the age of 12 years or weighing less than 43 kg body weight because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4).

Method of administration For rectal use.
The suppositories should be inserted deeply into the anus after bowel movement. They may be warmed in the hand or dipped into hot water to improve sliding properties.

The duration of use is determined by the physician.

4.3 Contraindications

Paracetamol/codeine must not be used in:

- hypersensitivity to the active substances, peanut, soya or to any of

the excipients listed in section 6.1
- respiratory insufficiency
- respiratory depression
- deep unconsciousness
- coma
- pneumonia
- acute asthma attack
- imminent birth
- imminent premature birth
- children below the age of 12 years
- all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions (see section 4.4)
- women during breastfeeding (see section 4.6)
- patients for whom it is known they are CYP2D6 ultra-rapid metabolisers

4.4 Special warnings and precautions for use

In order to avoid the risk of an overdose, one should make sure that concurrent medication does not contain paracetamol and/or codeine.

In the following cases paracetamol/codeine should be used after rigorous assessment of the risk/benefit balance

- opioid dependence
- impaired consciousness
- conditions associated with increased intracranial pressure
- disorders of the respiratory centre and respiratory function
- concomitant use of MAO inhibitors
- chronic obstructive pulmonary disease

In the following cases paracetamol/codeine should be used only with special caution (this means a prolonged dose interval or a reduced dose) and under medical supervision:
- hepatocellular insufficiency
- chronic alcohol abuse
- severe renal insufficiency (GFR < 30 ml/min) and dialysis patients
- Gilbert's syndrome
- concomitant intake of medicinal products that impair liver function
- disorders which can be accompanied by a reduced glutathione level (possibly dose adjustment e.g. with diabetes mellitus, HIV, Down syndrome, tumours)
- glucose-6-phosphate dehydrogenase deficiency
- dehydration
- haemolytic anaemia
- glutathione deficiency
- chronic malnutrition

- body weight below 50 kg
- elderly patients

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency of or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency.
However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine very rapidly, resulting in higher than expected plasma morphine levels.

Therefore, the response of the individual patient to the medicinal product should be monitored at the start of treatment in order to be able to detect potential relative overdoses rapidly. This applies particularly to elderly patients, to impaired renal function and to respiratory disorders (risk of pulmonary oedema).

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal (see section 4.9).

Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	*Prevalence %*
African/Ethiopian	29%
African American	3.4% to 6.5%
Asian	1.2% to 2%
Caucasian	3.6% to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1%-2%

Post-operative use in children

There have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, has led to rare, but life-threatening adverse events including death (see also section 4.3). All children received doses of codeine that were within the appropriate dose range; however, there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromised respiratory function
Paracetamol/codeine is not recommended for use in children in whom respiratory function might be compromised including due to neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Severe acute hypersensitivity reactions (e.g. anaphylactic shock) are very rarely observed. Treatment must be discontinued at the first signs of a hypersensitivity reaction after use/administration of paracetamol/codeine. Any medically necessary measures commensurate with the symptoms must be instigated by professional staff. The patient should be instructed to discontinue the medicinal product and to contact a physician immediately at the first signs of a hypersensitivity reaction.

The use of higher doses than recommended may result in severe liver damage.

If large amounts of paracetamol are used for extended periods of time and the drug is not used properly, it may cause headache, which should not be treated with increased doses. In such cases, the analgesic should not be continued without first seeking the advice of a medical practitioner.

In general, the habitual use of painkillers, particularly in combination with other painkillers (of the anti-inflammatory/antipyretic type), may lead to permanent kidney damage associated with the risk of renal failure (analgesic nephropathy).

Headache, fatigue, muscular pain, nervousness and vegetative symptoms may occur after abrupt discontinuation of any analgesic not used as directed or used in large doses over long periods of time. No analgesic should be used before subsidence of such symptoms, which usually disappear within a few days. A physician should be consulted before resuming treatment.

Use of the total daily dose of paracetamol as a single dose can lead to severe liver damage; medical advice should be sought immediately in this case.

This medicinal product should not be used at high doses in patients with hypotension and coexisting hypovolaemia.

As a component of this fixed combination, codeine may induce dependence. The long-term use of large amounts gives rise to drug tolerance and physical and psychological dependence. Cross-tolerance with other opioids has been observed. Persons with pre-existing opiate dependence (even in remission)

are likely to suffer a relapse within a short time.
Codeine is regarded as a substitute by heroin addicts. Subjects with alcohol dependence and sedative dependence also tend to abuse codeine.

Codeine-containing medicinal products may be used only on medical prescription and under constant medical supervision. No responsibility can be accepted for the passing on to third parties of medicinal products that have been prescribed for personal use.

Caution should be exercised in the treatment of patients who have previously undergone cholecystectomy. As a result of the contraction of the sphincter of Oddi, myocardial infarction-like symptoms can occur, as well as potentiation of the symptoms in the case of pre-existing pancreatitis.

If high doses are used or in the case of particularly sensitive patients, visuomotor co-ordination and visual performance can be impaired dose-dependently. Similarly, respiratory depression and euphoria can occur.

Risks of concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products:
Concomitant use of paracetamol/codeine and sedative medicinal products such as benzodiazepines or related medicinal products can lead to sedation, respiratory depression, coma and death. In view of these risks, co-prescribing with these sedative medicinal products is appropriate only in patients for whom no other treatment options exist. Nevertheless, if concomitant use of paracetamol/codeine with sedatives is considered necessary, the lowest effective dose should be used and the duration of treatment should be as short as possible. The patient should be closely monitored for signs and symptoms of respiratory depression and sedation. In this connection, it is strongly recommended that patients and their caregivers be informed about these symptoms (see section 4.5).

<u>Effect on laboratory values:</u>
The use of paracetamol can affect uric acid determination by means of phosphotungstic acid or blood sugar determination by means of glucose oxidase/peroxidase.

4.5 Interaction with other medicinal products and other forms of interaction

The sedative and respiratory-depressant effect may be potentiated by the concomitant use of other CNS depressants such as sedatives, hypnotics or psychotropic drugs (phenothiazines such as chlorpromazine, thioridazine, perphenazine), antihistamines (such as promethazine, meclizine), antihypertensives, other analgesics as well as alcohol.

Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of an additive CNS

depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

In patients who concomitantly receive drugs leading to enzyme induction in the liver, e.g. certain hypnotics and antiepileptics (such as phenobarbital, phenytoin, carbamazepine), or rifampicin, normally safe doses of paracetamol may cause liver damage.
The same applies to potentially hepatotoxic substances and alcohol abuse.

Patients who simultaneously receive paracetamol and zidovudine (AZT or Retrovir) may be more susceptible to the development of neutropenia.

Use of probenecid inhibits binding of paracetamol to glucuronic acid, thereby causing a reduction in paracetamol clearance by approx. a factor of 2. The dosage of paracetamol should be reduced when administered concomitantly with probenecid.

Cholestyramine reduces the absorption of paracetamol.

Alcohol should be avoided during treatment with paracetamol/codeine, as psychomotor performance is markedly reduced (via the additive effect of the individual components).

Codeine-induced respiratory depression can be potentiated by tricyclic antidepressants (imipramine, amitriptyline) and opipramol.

When MAO inhibitors, such as tranylcypromine, are used at the same time, an increase in central nervous effects and other side effects may be observed to an unforeseeable extent.
Paracetamol/codeine must therefore not be used until two weeks after the end of treatment with MAO inhibitors.

The action of analgesics is potentiated. When partial opioid agonists/antagonists such as buprenorphine or pentazocine are taken at the same time, a reduction in effect of the medicinal product is possible.

Cimetidine and other medicines that affect liver metabolism can increase the effect of paracetamol/codeine. During treatment with morphine, inhibition of the breakdown of morphine has been observed with a subsequent increase in plasma concentrations. An interaction of this kind cannot be ruled out for codeine.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risks factors (see section 4.4).

Repeat use of paracetamol over a period longer than one week potentiates the effect of anticoagulants, particularly warfarin. As a result, medical supervision is required for prolonged use of paracetamol in patients treated with anticoagulants. Occasional paracetamol use has no

significant effect on the bleeding tendency.

4.6 Fertility, pregnancy and lactation Pregnancy

An association was noted between malformations of the respiratory tract and the administration of codeine in the first three months of pregnancy. Indications of other malformations are also available from epidemiological studies with narcotic analgesics, including codeine. Paracetamol/codeine may therefore be used during pregnancy, particularly during the first three months, only if strictly indicated and after careful risk-benefit assessment.

Paracetamol/codeine is contraindicated if the patient is about to give birth or if there is an imminent risk of giving birth prematurely, since codeine crosses the placental barrier and can cause breathing disorders in new-borns.

If codeine is used for a prolonged period, codeine dependence can develop in the foetus.

There are reports of withdrawal symptoms in new-borns after repeated use of codeine in the last trimester of pregnancy.

Breast-feeding

Paracetamol/codeine is contraindicated in women during breast-feeding (see section 4.3).

Paracetamol and codeine as well as its metabolite morphine are excreted in human milk.

At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low concentrations and this is unlikely to adversely affect the breastfed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of potentially fatal opioid toxicity in the infant.

4.7 Effects on ability to drive and use machines

Even if used as directed, the codeine contained by this medicine can modify the patient's reactions impairing the ability to drive a motor vehicle or operate machinery.

4.8 Undesirable effects

Tabulated list of undesirable effects

In the following table, adverse reactions are listed by MedDRA system organ class and frequency.

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)

Blood and lymphatic system disorders	Rare	allergic thrombocytopenia, leukocytopenia
	Very rare	agranulocytosis, pancytopenia

Immune system disorders	Very rare	hypersensitivity reactions such as angioedema, dyspnoea, sweating, nausea, hypotension progressing to shock
Nervous system disorders	Very common	fatigue, mild headache
	Common	mild drowsiness
	Uncommon	sleep disturbances
Ear and labyrinth disorders	Uncommon	tinnitus
Vascular disorders	Common	after administration of high doses, hypotension, syncope
Respiratory, thoracic and mediastinal disorders	Uncommon	shortness of breath
	Very rare	bronchospasm (analgesic asthma) pulmonary oedema (at high doses, particularly in the presence of pre-existing pulmonary dysfunction)
Gastrointestinal disorders	Very common	nausea, vomiting (at the start of treatment), constipation
	Uncommon	dry mouth
Hepatobiliary disorders	Rare	increase in liver-specific laboratory values (increase in liver transaminases)
Skin and subcutaneous tissue disorders	Uncommon	pruritus, erythema, allergic exanthema, urticaria
	Rare	severe skin reactions, including Stevens-Johnson syndrome
Metabolism and nutrition disorders	Very rare	Post-marketing experience: cases of high anion gap metabolic acidosis have been reported with concomitant use of flucloxacillin and paracetamol, generally when risk factors were already present.

There is no evidence that, when used as directed, the fixed combination exacerbates or extends the spectrum and nature of the undesirable effects of the individual substances.

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.

4.9 Overdose

The symptoms and the treatment of an overdosage with paracetamol and codeine correspond to the symptoms of intoxication with the single agents.

Symptoms of intoxication

Paracetamol
There is a risk of intoxication, particularly in the elderly, small children, people suffering from liver disease, chronic alcohol abuse, chronic malnutrition and concomitant use of medications that cause enzyme induction. In such cases, an overdose can be fatal.
As a rule, symptoms occur within 24 hours: nausea, vomiting, anorexia, pallor and lower abdominal pain. Afterwards, the patient may feel better. However, mild abdominal pain remains indicating liver damage.
An overdose with approx. 6 g or more of paracetamol in a single dose in adults or with 140 mg/kg body weight as a single dose in children causes hepatic necrosis, which may progress to totally irreversible necrosis, and eventually to hepatocellular failure, metabolic acidosis and encephalopathy. These in turn may progress to a coma that can be fatal. At the same time, elevated liver transaminase levels (AST, ALT), lactate dehydrogenase and bilirubin in conjunction with elevated prothrombin, have been observed, which may occur 12 to 48 hours after use. Clinical symptoms of liver damage become apparent after 2 days as a rule and reach their peak after 4 to 6 days.
Acute renal failure associated with acute tubular necrosis may develop even in the absence of severe liver damage. Myocardial anomalies and pancreatitis are other non-liver-related symptoms that have been observed following an overdose with paracetamol.

Codeine
A characteristic symptom of codeine overdosage is respiratory depression. Somnolence including stupor and coma as well as vomiting, headache, urinary and faecal retention, in some cases bradycardia and hypotension have been observed. Seizure disorders have been reported occasionally, especially in children.
These symptoms can be potentiated by the concomitant intake of alcohol or central depressants. Codeine can increase smooth muscle tone, particularly at single doses of more than 60 mg.

Treatment of intoxication
Paracetamol

As soon as intoxication with paracetamol is suspected,

- measuring the plasma concentrations of paracetamol is advisable;
- dialysis can reduce the amount of paracetamol in the blood;
- sulfhydryl group donors, such as N-acetylcysteine should be administered intravenously in the first 10 hours. However, N-acetylcysteine may still offer a certain degree of protection even after 10 and for up to 48 hours. In this case, it should be taken for longer periods.

Further therapy options for treating intoxication with paracetamol are directed at the extent, stage and clinical symptoms commensurate with the standard treatment measures in intensive care medicine.

Codeine

In the event that amounts exceeding 2 mg of codeine per kg b.wt. have been ingested and if the patient develops clinical symptoms, respiration should be monitored and resuscitation should be available until subsidence of symptoms. In the absence of clinical symptoms, these measures should be taken for a period of up to six hours.

In case of manifest respiratory depression, the effects of codeine can be abolished by opiate antagonists such as naloxone

Naloxone must be given more than once, since the effect of codeine lasts longer than that of naloxone. If naloxone cannot be used, symptomatic measures should be adopted, above all lateral recumbent position, artificial respiration and shock therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Opioids in combination with non-opioid analgesics ATC code: N02AJ06

Paracetamol

Paracetamol is an analgesic and antipyretic having a very weak anti-inflammatory action; its mechanism of action is still not entirely clear.
It is well established that paracetamol inhibits central prostaglandin synthesis to a far greater extent than peripheral prostaglandin synthesis. Furthermore, it counteracts the effect of the endogenous pyrogens on the hypothalamic heat-regulating centre. It may be assumed that there is a correlation between this mechanism and its antipyretic action.

Codeine

Codeine is a phenanthrene alkaloid with opioid-agonist properties and it has a central analgesic and antitussive effect. The effect is dose-dependent and is partially mediated through binding to supraspinal opioid receptors (μ receptors), although codeine has extremely low affinity for opioid receptors. Part of the effect is mediated via the morphine metabolite.

In clinical studies, the association of paracetamol and codeine has been compared with various analgesics and with placebo. In all cases, the fixed dose mixture was shown to be superior to placebo. The difference was

statistically significant. The results of certain studies suggest that the combination produces a stronger analgesic effect than the single compounds, even after an increase in their doses, subject to acceptable risks.

5.2 Pharmacokinetic properties Paracetamol

Absorption:
When administered rectally, paracetamol is absorbed rapidly (0.5 – 1.5 hours to peak serum concentrations) and completely. Peak plasma levels are reached within 30 to 60 minutes after the administration of the drug.

Metabolism occurs primarily in the liver by direct conjugation with glucuronic acid or sulfuric acid. A small proportion of metabolism occurs via the cytochrome P450 system (predominantly CYP2E1)

with the formation of the toxic metabolite N-acetyl-p-benzoquinone imine, which is normally bound and excreted but which in the event of massive intoxication is markedly increased in concentration.

Elimination:
Excretion is renal. Ninety per cent of the ingested amount is excreted within 24 hours, predominantly as glucuronide (60 to 80%) and sulfate conjugates (20 to 30%), via the kidneys. Less than 5% is excreted in the unchanged form. The elimination half-life is about two hours. The half-life is prolonged in patients with impaired hepatic and renal function, following overdose and in new-borns. The peak effect and mean duration of action (4 to 6 hours) correlate approximately with the plasma concentration.

Renal impairment:
In patients with severe renal impairment (GFR < 30 ml/min), the elimination of paracetamol and its metabolites is delayed.

Codeine

Absorption:
Codeine is rapidly absorbed after rectal administration. Peak plasma levels are reached within about one hour.

The drug is metabolised in the liver (considerable variation among individuals). Morphine, norcodeine and conjugates of morphine and codeine are the main metabolites of the drug, the conjugate concentrations being considerably higher than those of the parent substances.

Elimination:
The elimination half-life of between 3 and 5 hours rises to 9 to 18 hours in subjects with renal failure. Excretion is also slower in the elderly. Codeine is excreted mainly by the kidney. About 10 percent is eliminated from the body unchanged.

Codeine crosses the placental barrier and enters the foetal blood circulation. Pharmacologically active concentrations have been detected in human milk after the administration of high codeine doses.

Paracetamol and codeine are comparable as regards absorption rates, times to peak plasma concentrations, approximately the same duration of action. The successive steps of their biotransformation and the renal elimination processes do not interfere with each other.

5.3 Preclinical and safety data

Paracetamol

In animal studies of the acute, subchronic and chronic toxicity of paracetamol in rats and mice, gastrointestinal lesions, blood count changes, degenerative changes of the hepatic and renal parenchyma and necrosis have been observed. The reason for these changes is to be sought, on the one hand, in the mechanism of action and, on the other, in the metabolism of paracetamol. The metabolites that are the putative cause of the toxic effect and the resultant change in organs have also been found in humans. Very rare cases of reversible chronic aggressive hepatitis have also been observed during long-term use (i.e. 1 year) in the range of maximum therapeutic doses.
At subtoxic doses, symptoms of intoxication can occur after three weeks of administration. Paracetamol should therefore not be used for prolonged periods and at high doses.

Extensive studies have revealed no evidence of a relevant genotoxic risk of paracetamol in the therapeutic, i.e. non-toxic, dose range.

Long-term studies in rats and mice have not revealed any evidence of relevant carcinogenic effects at non-hepatotoxic doses of paracetamol.

Paracetamol crosses the placenta.

No conventional studies are available in which currently accepted standards to assess toxicity to reproduction and development were used.

Codeine

In vitro and *in vivo* studies with codeine have revealed no evidence of mutagenic potential.
Long-term studies in rats and mice have revealed no evidence of a carcinogenic potential of codeine. There is evidence of teratogenic potential from animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard fat, soya lecithin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 30ºC.
Protect from light.

6.5 Nature and contents of container

Aluminium strips coated with polyethylene Pack size: 10 suppositories

6.6 Special precautions for disposal

No special requirements.

7. Marketing authorisation holder

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675
München
Germany

8. Marketing authorisation number

H2008/18955/091/R1

9. Date of first authorisation

29/03/2026

10. DATE OF REVISION OF THE TEXT

10/2022