Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Solpadol Caplets 500 mg/30 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Paracetamol 500.0 mg
Codeine Phosphate Hemihydrate 30.0 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White to off-white capsule-shaped tablet with flat sides marked 'SOLPADOL' on one side and blank on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of severe pain in adults.

Solpadol is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

4.2 Posology and method of administration

Solpadol should be used at the lowest effective dose for the shortest period of time. This dose may be taken, up to 4 times a day at intervals of not less than 6 hours. Maximum daily dose of codeine should not exceed 240mg.

The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

Adults (18 years and over):
Two tablets every 4-6 hours to a maximum of four doses in any 24 hours.
Do not exceed eight tablets in 24 hours.

Elderly:
The initial dosage should be reduced to half the recommended dosage and should be titrated to the individuals need and overall medical condition.

Paediatric Population

Children aged 16 to 18 years:
One to two tablets every 6 hours to a maximum of four doses in any 24 hours.
Do not exceed 8 tablets in 24 hours.

Children (12-15 years):
One tablet every 6 hours to a maximum of four doses in any 24 hours.
Do not exceed 4 tablets in 24 hours.

Children aged less than 12 years:
Solpadol should not be used in children below the age of 12 years 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).

In patients with renal failure (creatinine clearance lower than 10 ml/min), the interval between two doses should be at least 8 hours.

Renal impairment:
It is recommended, when giving paracetamol to patients with renal impairment, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours unless directed otherwise by a physician. See Table below:

Glomerular filtration rate	Dose
10-50 ml/min	500mg every 6 hours
<10ml/min	500mg every 8 hours

Hepatic Impairment:
In patients with impaired hepatic function or Gilbert's Syndrome, the dose must be reduced or the dosing interval prolonged. The daily dose of paracetamol should not exceed 2g/day unless directed by a physician.

The maximum daily dose of paracetamol should not exceed 60mg/kg/day (up to a maximum of 2g per day) in the following situations, unless directed by a physician:

- Weight less than 50kg
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

Solpadol Caplets are for oral administration.

4.3 Contraindications

In 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).

In the event of impending childbirth or in case of risk of premature birth (see section 4.6).

In women during breastfeeding (see section 4.6).

In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

In patients hypersensitive to paracetamol or codeine, or hypersensitivity to any of the other constituents.

In patients with acute asthma, respiratory depression, acute alcoholism, head injuries, raised intra-cranial pressure and following biliary tract surgery.

In patients currently receiving or within 14 days of stopping monoamine oxidase inhibitor therapy.

4.4 Special warnings and precautions for use

Paracetamol should be administered with caution under the following circumstances (see section 4.2 where relevant):

- Hepatic impairment
- Chronic alcoholism
- Renal impairment (GFR≤50ml/min)
- Gilbert's Syndrome (familial non-haemolytic jaundice)
- Concomitant treatment with medicinal products affecting hepatic function

- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition
- Weight less than 50kg
- Elderly

Solpadol should be used after careful risk-benefit assessment in case of:

- Opioid dependence
- Chronic constipation
- Impaired consciousness
- Compromised respiratory function and chronic obstructive airway disease

CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency 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 rapidly resulting in higher than expected serum morphine levels.

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.

Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized 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% to 2%

Risks from concomitant use of opioids and benzodiazepines:

Concomitant use of opioids, including codeine, with benzodiazepines may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe codeine concomitantly with benzodiazepines, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of sedation and respiratory depression (see Section 4.5).

Risks from concomitant use of opioids and alcohol:

Concomitant use of opioids, including codeine, with alcohol may result in sedation, respiratory depression, coma, and death. Concomitant use with alcohol is not recommended (see Section 4.5).

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, 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 ultrarapid or extensive metabolisers in their ability to metabolise codeine to morphine.

Children with compromise drespiratory function
Codeine is not recommended for use in children in whom respiratory function might be compromised including 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.

Solpadol should be administered with caution in certain patients, such as those with impaired cardiac, hepatic or renal function, hypotension, benign prostatic hyperplasia, urethral stenosis, adrenal insufficiency (Addison's disease), hypothyroidism, multiple sclerosis, chronic colitis ulcerative, and diseases that present with reduced respiratory capacity such as emphysema, kyphoscoliosis and severe obesity.

This product should only be used with great care in any patient whose condition may be exacerbated by opioids, such as those who are on concurrent CNS drugs, those with prostatic hypertrophy or those with inflammatory or obstructive bowel disorders. Care should also be observed if prolonged therapy is contemplated.

Extensive use of analgesics to relieve headaches or migraines, especially at high doses, may induce headaches that must not be treated with increased doses of the drug. In such cases the analgesic should not continue to be taken without medical advice.

Use with caution in patients with convulsive disorders.

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with alcoholic liver disease. In patients with kidney failure (creatinine clearance lower than 10 ml/min): the interval between doses should be increased (minimum 8 hours). See section 4.2.

Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction (See Section 4.8)

Caution is advised in patients with underlying sensitivity to aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs).

Severe-cutaneous adverse reactions (SCARs): Very rare cases of serious skin reactions such as Stevens-Johnson syndrome (SJS), and Toxic epidermal necrolysis (TEN) have been reported with the use of paracetamol. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms or signs of SJS and TEN (e.g. progressive skin rash often with blisters or mucosal lesions) occur, patients should stop immediately Solpadol treatment and seek medical advice.

Patients should be advised not to exceed the recommended dose and not take other paracetamol containing products concurrently.

Codeine has a primary potential for dependence. Tolerance, psychological and physical dependence (addiction) develop with prolonged use of high doses with withdrawal symptoms, such as restlessness and irritability, after sudden discontinuation of the drug. Cross-tolerance with other opioids exists. Rapid relapses can be expected in patients with pre-existing opiate dependence (including those in remission). Administration must be discontinued gradually after prolonged treatments.

There have been reports of drug abuse with codeine, including cases in children and adolescents. Caution is particularly recommended for use in children, adolescents, young adults and in patients with a history of drug and/or alcohol abuse.

The risk-benefit of continued use should be assessed regularly by the prescriber.

Monitoring after prolonged use should include blood count, liver function and renal function.

In patients who have had a cholecystectomy, codeine may induce acute biliary or pancreatic abdominal pain, which usually occurs with abnormal laboratory results, suggesting a spasm of the sphincter of Oddi. Solpadol is contraindicated for use in these patients. Section 4.3.

If the patient has a productive cough, codeine may impede expectoration.
Elderly patients may be more sensitive to the effects of this medicinal product, especially respiratory depression; they are also more prone to suffering hypertrophy, prostatic obstruction and age-related kidney impairment and they have a higher likelihood of undesirable effects due to opioid-induced urinary retention

Elderly patients: the initial dosage should be reduced to half the recommended dosage; this may be later increased based on patient tolerance and needs. See section 4.2

In ultra-rapid opiate/codeine metabolisers, there is an increased risk of developing opioid toxicity even at low doses. Symptoms of opioid toxicity include nausea, vomiting, constipation, lack of appetite and somnolence. In severe cases this may include symptoms of circulatory and respiratory depression.

Cases of high anion gap metabolic acidosis (HAMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe 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.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol may increase the elimination half-life of chloramphenicol. Oral contraceptives may increase its rate of clearance. Thespeed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by colestyramine.

The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes, such as antiepileptics (such as phenobarbital, phenytoin, carbamazepine, topiramate), rifampicin and alcohol.

Paracetamol may increase the risk of bleeding in patients taking warfarin, antivitamin K and other coumarins. These patients should be monitored for appropriate coagulation and bleeding complications.

Co-administration of flucloxacillin with paracetamol may lead to metabolic acidosis, particularly in patients presenting risk factors of glutathione depletion, such as sepsis, malnutrition or chronic alcoholism.

Chelating resin can decrease the intestinal absorption of paracetamol and potentially decrease its efficacy if taken simultaneously. In general, there must be an interval of more than 2 hours between taking the resin and taking paracetamol, if possible.
Treatment with paracetamol may interfere with the assay of blood uric acid by the phosphotungstic acid method. Treatment with paracetamol may interfere with the assay of blood glucose when concentrations are abnormally high.

Benzodiazepines and Opioids:
The concomitant use of benzodiazepines and opioids increases the risk of sedation, respiratory depression, coma, and death, because of additive CNS depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see Section 4.4).

Alcoholand Opioids:
The concomitant use of alcohol and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect. Concomitant use with alcohol is not recommended (see Section 4.4).

Tricyclic antidepressants
A codeine-induced respiratory depression can be potentiated by tricyclic antidepressants.

Mono Amine Oxidase Inhibitors (MAOI's)
Concomitant administration of MAOI can potentiate the central nervous effects and other side effects of unpredictable severity. Solpadol should not be used in patients currently receiving or within 14 days of stopping monoamine oxidase inhibitor therapy. See section 4.3.

Antiperistaltic antidiarrhoeal drugs
Concomitant use of codeine with antiperistaltic antidiarrhoeal drugs can increase the risk of severe constipation and CNS depression.

Inadvisable combinations with codeine
Morphine agonists-antagonists (buprenorphine, nalbuphine, pentazocine): Reduced analgesic effect due to competitive receptor blockade, with a risk of withdrawal syndrome.

Naltrexone: Risk of reduced analgesic effect. The doses of the morphine derivative should be increased if necessary.
Combinations to be taken into account:
Patients receiving other narcotic analgesics, antitussive, antihypertensives, antihistamines, antipsychotics, antianxiety agents, benzodiazepines, barbituates, methadone or other CNS depressants (including alcohol) concomitantly with this codeine containing drug may exhibit additive CNS depression including increased risk of respiratory depression.

CYP2D6 inhibitors
Codeine is metabolized by the liver enzyme CYP2D6 to its active metabolite morphine. Medicines that inhibit CYP2D6 activity may reduce the analgesic effect of codeine. Patients taking codeine and moderate to strong CYP2D6 inhibitors (such as quinidine, fluoxetine, paroxetine, bupropion, cinacalcet, methadone) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

CYP3A4 inducers
Medicines that induce CYP3A4 activity may reduce the analgesic effect of codeine. Patients taking codeine and CYP3A4 inducers (such as rifampin) should be adequately monitored for reduced efficacy and withdrawal signs and symptoms. If necessary, an adjustment of the treatment should be considered.

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)

4.6 Fertility, pregnancy and lactation

Pregnancy
Solpadol should not be used in pregnancy.
Codeine can cause respiratory depression and withdrawal syndrome in newborns.

Breastfeeding
Solpadol should not be used during breastfeeding (see Section 4.3).
Codeine and paracetamol are excreted in breast milk.

Codeine is partially metabolized by cytochrome P450 2D6 (CYP2D6) into morphine, which is excreted into breast milk. If nursing mothers are CYP2D6 ultra-rapid metabolisers, higher levels of morphine may be present in their breast milk. This may result in symptoms of opioid toxicity in both mother and the breast-fed infant.
Life-threatening adverse events or neonatal death may occur even at therapeutic doses.

Paracetamol
A large amount of data on the use of paracetamol in pregnancy indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results.

4.7 Effects on ability to drive and use machines

Solpadol may cause drowsiness, disturbances of visuomotor coordination and visual acuity, impairing the mental and/or physical ability required for the performance of potentially dangerous tasks, such as driving vehicles or using machines.

4.8 Undesirable effects

MedDRA Organ system classes	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 frequency cannot be estimated from the available data
Related to Paracetamol					

Blood and lymphatic system disorders				Thrombocytopenia, neutropenia, leukopenia	Agranulocytosis, haemolytic anaemia, in particular in patients with underlying glucose 6-phosphate- dehydrogenase
Immune system disorders					Hypersensitivity such as anaphylactic shock, angioedema
Respiratory, thoracic and mediastinal disorders					Bronchospasm
Skin and subcutaneous disorders				Erythema, urticaria, rash	Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis, fixed drug eruption
Hepatobiliary disorders					Cytolytic hepatitis, which may lead to acute hepatic failure
Metabolism and nutrition system disorders					High anion gap analysis. Pyroglutamic acidosis, inpatients with pre-disposing factors for glutathione depletion
Related to Codeine					
Immune system disorders					Hypersensitivity
Psychiatric disorders					Confusional state, dysphoria, euphoria. Long term use also entails the risk of drug dependence.
Nervous system disorders					Seizure, headache, somnolence, dizziness, sedation
Eye disorders					Miosis, visuomotor coordination and visual acuity may be adversely affected in a dose- dependent manner at higher doses or in particularly sensitive patients
Ear and labyrinth disorders					Tinnitus
Respiratory, thoracic and mediastinal disorders					Respiratory depression
Gastrointestinal disorders					Constipation, vomiting, nausea, dry mouth
Skin and subcutaneous tissue disorders					Pruritus
Renal and urinary disorders					Urinary retention
General disorders and administration site conditions					Fatigue
Vascular disorders					Hypotension

Description of selected adverse reactions

High anion gap metabolic acidosis

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.

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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Paracetamol
Paracetamol overdose can result in liver damage which may be fatal.

Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.
Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis, disseminated intravascular coagulation, and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.
Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue.
Some patients may be at increased risk of liver damage from paracetamol toxicity:

Risk factors include:

- Patients with liver disease
- Elderly patients
- Young children
- Patients receiving long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Patients who regularly consume ethanol in excess of recommended amounts
- Patients with glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Acute renal failure with acute tubular necrosis may also develop.

Cardiac arrhythmias and pancreatitis have also been reported.

Emergency Procedure:

Immediate transfer to hospital.

Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. Administration of activated charcoal should be considered if the overdose of paracetamol has been ingested within the previous hour.

The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines.

Symptomatic treatment should be implemented.

Codeine

The effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.

Symptoms:

Central nervous system depression, including respiratory depression, may develop but is unlikely to be severe unless other sedative agents have been co-ingested, including alcohol, or the overdose is very large. The pupils may be pin-point in size; nausea and vomiting are common. Hypotension, rash, pruritis, ataxia, pulmonary edema (more rare) are possible.

The ingestion of very high doses can cause initial excitation, anxiety, insomnia followed by drowsiness in certain cases, areflexia progressing to stupor or coma, headache, miosis, alterations in blood pressure, arrhythmias, dry mouth, hypersensitivity reactions, cold clammy skin, bradycardia, tachycardia, convulsions, gastrointestinal disorders, nausea, vomiting and respiratory depression.

Severe intoxication can lead to apnoea, circulatory collapse, cardiac arrest and death.

Management:
Respiratory assistance: This should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. Consider activated charcoal if an adult presents within one hour of ingestion of more than 350 mg or a child more than 5 mg/kg.

Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half-life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anilides, Paracetamol combinations.
ATC Code: N02AJ06.

Paracetamol is an analgesic which acts peripherally, probably by blocking impulse generation at the bradykinin sensitive chemo-receptors which evoke pain. Although it is a prostaglandin synthetase inhibitor, the synthetase system in the CNS rather than the periphery appears to be more sensitive to it. This may explain paracetamol's lack of appreciable anti-inflammatory activity. Paracetamol also exhibits antipyretic activity.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

5.2 Pharmacokinetic properties

Following oral administration of two tablets (i.e. a dose of paracetamol 1000mg and codeine phosphate 60mg) the mean maximum plasma concentrations of paracetamol and codeine were 15.96μg/ml and 212.4ng/ml respectively. The mean times to maximum plasma concentrations were 0.88 hours for paracetamol 1.05 hours for codeine phosphate.

The mean AUC for the 9 hours following administration was 49.05$\mu g.ml^{-1}.h$ for paracetamol and 885.0$ng.ml^{-1}.h$ for codeine.

The bioavailabilities of paracetamol and codeine phosphate when given as the combination are similar to those when they are given separately.

5.3 Preclinical safety data

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

Pregelatinised starch
Maize starch
Providone
Potassium sorbate
Microcrystalline celulose
Stearic acid
Talc
Magnesium sterate
Croscarmellose sodium

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

1) Amber glass bottles with tinplate screw cap with steran-faced plupboard wad.
2) PVC/aluminum foil (250 µm/20 µm) or PVC/aluminium foil (250 µm/20 µm)/PVC (15 µm) blister packs or PVC/aluminium foil (250 µm/9 µm)/Glassine paper (35 gsm).
Pack of 4, 10, 60 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Phoenix Labs
Suite 12, Bunkilla Plaza
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Clonee
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Ireland

8 MARKETING AUTHORISATION NUMBER

PA1113/027/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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