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Cevimeline

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Contents

Abstract

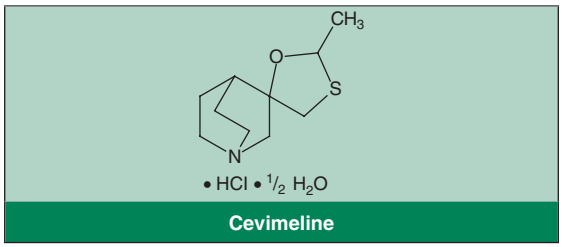
▲ Cevimeline is an orally administered muscarinic receptor agonist that is indicated for the treatment of symptoms of dry mouth in patients with Sjögren's syndrome.

▲ Several well designed placebo-controlled trials demonstrated that 4–12 weeks' therapy with cevimeline 30 mg three times daily improved symptoms of dry mouth in patients with Sjögren's syndrome. Other symptoms, such as dry eye symptoms and overall dryness, also improved to a significantly greater extent with cevimeline than with placebo. Moreover, cevimeline significantly improved the salivary flow rate in patients with Sjögren's syndrome.

▲ Increased salivary flow was maintained in the longer term with cevimeline in patients with Sjögren's syndrome and symptoms of dry mouth, according to the results of an open-label 52-week study. From week 20 onwards, rates of patient and investigator satisfaction with the cevimeline dosage were ≥88%.

▲ Oral cevimeline 30 mg three times daily was generally well tolerated in patients with Sjögren's syndrome, with many of the most commonly reported adverse events reflecting the pharmacological action of the drug.

Features and properties of cevimeline (FKS-508, SNI-2011, Evoxac®)	
Indication	
Treatment of symptoms of dry mouth in patients with Sjögren's syndrome	
Mechanism of action	
Muscarinic receptor agonist	Direct stimulation of muscarinic receptors in the salivary glands, inducing salivation
Dosage and administration	
Dose	30 mg
Route of administration	Oral
Frequency of administration	Three times daily
Pharmacokinetic profile of cevimeline 30 mg in women with Sjögren's syndrome	
Mean maximum plasma concentration (C_{max})	91.6 ng/mL
Mean time to C_{max}	1.5 h
Mean area under the plasma concentration-time curve from time zero to infinity	711.1 ng • h/mL
Mean elimination half-life	5.1 h
Adverse events associated with muscarinic agonism	
Nausea, increased sweating, rhinitis, diarrhoea	



Cevimeline

Sjögren's syndrome is a chronic autoimmune disorder that affects 0.5–1% of the population.[1,2] It is most prevalent in middle-aged women,[1,2] with a female to male ratio of nine to one.[3]

The defining characteristic of Sjögren's syndrome is lymphocytic infiltration of the exocrine glands.[2,4] As well as involving the salivary and lacrimal glands, which results in the classic symptoms of dry mouth and eyes, exocrine glands throughout the rest of the gastrointestinal system, the upper and lower respiratory systems, the skin and the vagina are affected.[4,5] Lymphocytic infiltration is limited to the exocrine glands in primary Sjögren's syndrome, whereas the exocrine involvement in secondary Sjögren's syndrome is associated with other autoimmune or connective tissue disorders, including rheumatoid arthritis and systemic lupus erythematosus.[4,5] Sjögren's syndrome can significantly impair the quality of life of patients.[1] For example, hyposalivation is associated with a parched mouth, dry and cracked lips, difficulty in chewing and swallowing dry foods, dental caries and fungal infection.[2,6] Serious complications associated with Sjögren's syndrome include interstitial pneumonia, nephritis and lymphoma.[4]

The main focus of therapy in Sjögren's syndrome is the improvement of symptoms such as dry mouth and eyes.[1] Therapy commonly consists of eye lubricants, saliva substitutes and pharmacological stimulators of secretory function.[1] The first secretagogue with demonstrable efficacy in the improvement of Sjögren's syndrome symptoms was the muscarinic receptor agonist pilocarpine.[1] However, pilocarpine is short-acting, necessitating frequent administration, which may limit its usefulness in the treatment of Sjögren's syndrome symptoms.[6,7]

Cevimeline (Evoxac®)[1] is an orally administered muscarinic receptor agonist that is available in several countries (including Japan, Taiwan and the US) for the treatment of symptoms of dry mouth in patients with Sjögren's syndrome. This article summarizes the pharmacological properties of cevimeline and reviews its clinical efficacy and tolerability in patients with Sjögren's syndrome and dry mouth symptoms.

1. Pharmacodynamic Profile

- Cevimeline is a quinuclidine derivative of acetylcholine that acts as a muscarinic receptor agonist.[8,9] It appears that direct stimulation by cevimeline of muscarinic M_3 receptors in the salivary glands is mainly responsible for the sialogogic effects of the drug.[10] Cevimeline inhibited the binding of [^{3}H]quinuclidinyl benzilate to rat submandibular/sublingual gland membranes with an apparent dissociation constant of 1.2 μmol/L.[11]
- Marked salivary secretion was seen in healthy men who received single doses of cevimeline 30–50 mg;[12] salivary secretion peaked 1–3 hours after administration of cevimeline.[13] Ninety minutes after administration of a single oral dose of cevimeline 30 mg to 12 women with Sjögren's syndrome, the salivary flow rate had significantly ($p = 0.0496$) increased from 0.04 mL/min at baseline to 0.13 mL/min.[8]
- Cevimeline also induced saliva secretion in various animal studies,[9-11,14-16] including animal models of Sjögren's syndrome,[11,14] with an effective dose in mice and rats of ≈3–10 mg/kg.[10,11,14,16] Repeat administration of cevimeline was not associated with tolerance in rats.[11]
- Cevimeline was ≈25 times less potent than pilocarpine, according to dose-response curves for the volume of saliva secreted in rats.[10] In addition, the saliva secretion induced by cevimeline was longer lasting than that induced by pilocarpine; salivation lasted 1.4- to 1.8-fold longer with cevimeline than

1 The use of trade names is for product identification purposes only and does not imply endorsement.

with pilocarpine in rats and ≈2-fold longer with cevimeline than with pilocarpine in dogs.[9]

- Studies in rats demonstrated that cevimeline also stimulated tear secretion,[11] but it did not induce increased water intake at doses sufficient to induce salivary secretion.[15]
- In animal studies, cevimeline doses sufficient to induce salivation (e.g. oral administration of 3–10 mg/kg) generally did not affect general behaviour,[17] the CNS,[16,17] the somatic nervous system,[18] or the respiratory,[16,19] cardiovascular,[16,19] gastrointestinal,[20] urinary[20] or reproductive[20] systems. Some deleterious effects (e.g. hypothermia, bradycardia) were seen at ≈10-fold higher doses and sometimes with alternative (e.g. intravenous) routes of administration.[16-20] Oral cevimeline at doses of ≥10 mg/kg was associated with mydriasis in mice and rats.[17,18]
- In terms of potential pharmacodynamic drug interactions, patients already receiving β-adrenoceptor antagonists should be administered cevimeline with caution, because of the possibility of conduction disturbances.[21] Additive effects may be seen if cevimeline is co-administered with drugs with parasympathomimetic effects.[21] Moreover, cevimeline may interfere with the actions of drugs with desirable antimuscarinic effects.[21]

2. Pharmacokinetic Profile

- A mean maximum plasma cevimeline concentration (C_{max}) of 59.9 ng/mL was reached in a mean 1.8 hours in healthy volunteers receiving cevimeline 30 mg three times daily for 7 days.[12] No accumulation of cevimeline or its metabolites occurred after repeat administration.[21]
- In healthy elderly volunteers (aged 62–80 years) who received cevimeline 30 mg, a mean C_{max} of 90.8 ng/mL was reached in a mean of 1.5 hours with a mean area under the plasma concentration-time curve from time zero to infinity (AUC_∞) of 774.6 ng • h/mL, and in women with Sjögren's syndrome who received cevimeline 30 mg, a mean C_{max} of 91.6 ng/mL was reached in a mean of 1.5 hours, with a mean AUC_∞ of 711.1 ng • h/mL.[13]
- Administering cevimeline with food slowed the rate of absorption, with a time to C_{max} of 1.53 hours in the fasting state and 2.86 hours after a meal; C_{max} was reduced by 17.3% with food.[21]
- The volume of distribution of cevimeline was ≈6 L/kg with plasma protein binding of <20%.[21]
- Cevimeline is metabolized by the cytochrome P450 (CYP) isozymes CYP2D6 and CYP3A3/4.[21] In the 24 hours after administration of a single dose of cevimeline 30 mg, 87% of the cevimeline dose was recovered, with 16.0% recovered as unchanged drug, 35.8% as trans-sulfoxide, 8.7% as cis-sulfoxide, 14.6% as the glucuronic acid conjugate of cevimeline, 7.7% as the glucuronic acid conjugate of the trans-sulfoxide metabolite and 4.1% as the N-oxide of cevimeline.[22] The trans- and cis-sulfoxide metabolites are not thought to contribute to the pharmacological activity of cevimeline.[23]
- Cevimeline 30 mg three times daily had a mean elimination half-life ($t_{1/2}\beta$) of 3.3 hours in healthy volunteers.[12] A mean $t_{1/2}\beta$ of 5.1 hours was seen in women with Sjögren's syndrome who received cevimeline 30 mg.[13]
- In healthy men who were administered a single dose of radiolabelled cevimeline 30 mg, 86.8% of the dose was recovered in the urine after 24 hours.[22] After 7 days, 97.3% of the dose was excreted in the urine and 0.5% was excreted in the faeces.[22]
- The pharmacokinetics of cevimeline in patients with renal or hepatic impairment have not been examined, nor have the effects of ethnicity on the pharmacokinetics of the drug.[21]
- In terms of potential pharmacokinetic drug interactions, inhibitors of CYP2D6 and CYP3A3/4 may inhibit the metabolism of cevimeline.[21] Cevimeline should be administered with caution to patients who are known or suspected to be deficient in CYP2D6 activity.[21] *In vitro*, cevimeline did not inhibit CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4.[21]

3. Therapeutic Efficacy

This section focuses on the results of well designed, placebo-controlled studies examining the

efficacy of cevimeline in the treatment of dry mouth symptoms in patients with Sjögren's syndrome. An early dose-finding study found the optimal cevimeline dosage to be 30 mg three times daily in this indication;[24] however, neither the results of this dose-finding study[24] nor those of small, open-label trials[25,26] are discussed further.

Comparisons with Placebo

The efficacy of oral cevimeline in the treatment of symptoms of dry mouth in patients with Sjögren's syndrome (n = 50–212) was examined in randomized, double-blind trials of parallel-group[27-30] or crossover[31] design. All but one[31] of the trials were multicentre. Three of these trials were conducted in the US;[27-29] data from one of the US trials were obtained from a US FDA review document.[29] One trial was conducted in China[31] and one was conducted in Japan (limited data are available from the Japanese trial).[30]

Where specified, the trials included adults who had primary or secondary Sjögren's syndrome with associated lacrimal and salivary gland dysfunction;[27-29,31] symptoms were of mild to moderate[28] or mild to severe[27,29] severity. Primary Sjögren's syndrome was defined as at least one positive response to ocular and oral symptom questions; lacrimal and salivary gland dysfunction; and positive anti-Ro/SS-A or anti-La/SS-B antibodies, rheumatoid factor, or anti-nuclear antibodies.[27-29] Secondary Sjögren's syndrome was defined as at least one positive response to ocular or oral symptom questions; lacrimal and salivary gland dysfunction; positive anti-Ro/SS-A or anti-La/SS-B antibodies, rheumatoid factor, or anti-nuclear antibodies; and evidence of accompanying rheumatoid arthritis or other connective tissue disease.[27-29] Lacrimal dysfunction was defined as abnormal Schirmer test results (≤5 mm in 5 minutes) for both eyes, and salivary dysfunction was defined as unstimulated whole saliva collection of ≤1.5 mL in 15 minutes.[27-29]

In the US studies, patients received cevimeline 30 or 60 mg three times daily or placebo for 6 weeks,[27] or cevimeline 15 or 30 mg three times daily or placebo for 12 weeks;[28,29] in the Japanese study, patients received cevimeline 30 mg three times daily or placebo for 4 weeks;[30] and in the Chinese study, patients received cevimeline 30 mg three times daily and placebo for 10 weeks each in a crossover manner.[31] This section focuses on results pertaining to the approved dosage of cevimeline 30 mg three times daily.

Where specified, mean patient age was 53.7–56.3 years.[27-30] In each trial, the majority of participants were women (87–100% of total population).[27-31]

In the US studies, primary endpoints were subjectively assessed by patients and included global evaluation of dry mouth,[27-29] dry eyes[27,28] and overall dryness,[27,28] (assessed as being 'better', 'no change' or 'worse' compared with baseline[27-29]), and assessment on a 100 mm visual analogue scale (VAS) of six dry mouth measures (feeling of the mouth, dryness of mouth, dryness of tongue, ability to speak without drinking, ability to chew and swallow food, and ability to sleep).[27] Secondary endpoints included assessment on a 100 mm VAS of dry mouth measures[28,29] and objective measurement of salivary flow.[27-29]

Endpoints assessed in the Chinese trial included scores on the Xerostomia Inventory (XI) [scored from 11 to 55 with higher scores indicating more severe dry mouth symptoms], the General Oral Health Assessment Index (GOHAI) [scored from 12 to 60 with higher scores indicating better oral health status], the Ocular Surface Disease Index (OSDI) [scored from 0 to 100 with higher scores indicating greater disability], and the Medical Outcomes Short Form (SF-36) questionnaire (with higher scores indicating better health status), and sialometry.[31] Endpoints assessed in the Japanese trial included salivary flow, dry mouth symptoms and an evaluation of global usefulness.[30]

Where specified, efficacy analyses were conducted in the intent-to-treat population using last observation carried forward analysis.[27-29]

Dry Mouth

- Oral cevimeline generally improved symptoms of dry mouth in patients with Sjögren's syndrome. At the final visit, a significantly greater proportion

of cevimeline 30 mg three times daily than placebo recipients reported an improvement in dry mouth symptoms (i.e. rated symptoms as 'better') in the 6-week (76% vs 35%; p = 0.004)[27] and one of the 12-week (66% vs 37%; p = 0.0004)[28] US studies. However, in the other 12-week US study, there was no significant difference between cevimeline 30 mg three times daily recipients and placebo recipients in the proportion of patients reporting their symptoms as 'better' at study end (53% vs 55%); this study was noted to have a high placebo response rate.[29]

- In one 12-week study,[28] the mean change from baseline to study end in VAS scores assessing dry mouth significantly favoured patients receiving cevimeline 30 mg three times daily versus placebo for the symptoms of feeling of the mouth (−22.3 vs −12.2; p = 0.0428), dryness of mouth (−27.0 vs −15.0; p = 0.0389) and ability to speak without drinking (−17.3 vs −6.2; p = 0.0125). However, in the other 12-week study, there was no significant difference between cevimeline 30 mg three times daily and placebo for any of the dry mouth VAS scores at study end.[29]

- In the 6-week study, the mean reductions from baseline to study end in VAS scores for the ability to speak without drinking (−12.0 vs −0.4; p = 0.01) and the ability to chew and swallow food (−13.2 vs −2.8; p = 0.02) were significantly greater with cevimeline 30 mg three times daily than with placebo.[27] However, there were no significant differences between cevimeline 30 mg three times daily recipients and placebo recipients in the change from baseline to study end in the VAS scores for feeling of the mouth or dryness of mouth.[27]

- In the Chinese trial, mean XI scores decreased from baseline to a significant extent with cevimeline after 10 weeks' therapy (from 34.3 to 31.7; p = 0.001) but not with placebo (from 34.3 to 33.4).[31] In addition, mean GOHAI scores increased from baseline to a significant extent with cevimeline (from 41.6 to 43.0; p = 0.029) but not with placebo (from 43.3 to 43.2).

- In the Japanese trial, a significantly greater proportion of cevimeline 30 mg three times daily than placebo recipients reported an improvement in the dry mouth symptoms of dry feeling (34% vs 11%; p < 0.001) and feeding difficulty (24% vs 10%; p = 0.032).[30]

Salivary Flow

- Cevimeline significantly improved the salivary flow rate in patients with Sjögren's syndrome. The increase from the predose to the postdose salivary flow rate was significantly greater with cevimeline 30 mg three times daily than with placebo at each follow-up visit in 6-[27] and 12-week[29] US studies. At the final visit, the mean changes with cevimeline 30 mg three times daily and placebo were 0.194 versus 0.015 mL/min (p = 0.007) in the 6-week study[27] and 0.135 versus 0.029 mL/min in the 12-week study (p = 0.0017).[29]

- Similarly, the change from the baseline salivary flow rate to the postdose salivary flow rate after 12 weeks' therapy was significantly (p = 0.007) greater with cevimeline 30 mg three times daily than with placebo in the third US study.[28] In addition, at study end, the postdose salivary flow rate was significantly (p = 0.0068) higher with cevimeline 30 mg three times daily than with placebo.[28]

- In the Japanese trial, salivary flow increased to a significantly greater extent with cevimeline 30 mg three times daily than with placebo (0.514 vs 0.288 g/2 min; p = 0.005).[30]

- By contrast, in the crossover study, cevimeline did not increase salivary flow rates from baseline to a significant extent, and there was no significant difference between cevimeline and placebo in salivary flow rates.[31]

Other Symptoms

- A significantly greater proportion of patients receiving cevimeline 30 mg three times daily versus placebo reported an improvement in dry eye symptoms (i.e. rated symptoms as 'better') after 6 (72% vs 30%; p = 0.007)[27] or 12 (39% vs 24%; p = 0.0453)[28] weeks of therapy in two US studies. In the 6-week study, the mean reduction from baseline to study end in the VAS score for the sand sensation in the eyes was significantly greater with cevimeline 30 mg three times daily than with placebo (−6.5 vs +4.2; p = 0.03).[27]

- Significantly more recipients of cevimeline 30 mg three times daily than placebo reported an improvement in overall dryness (i.e. rated symptoms as 'better') after 6 (75% vs 35%; p = 0.004) [values estimated from a graph][27] or 12 (66% vs 36%; p = 0.0003)[28] weeks of therapy.
- In the Chinese trial, cevimeline did not alter OSDI or SF-36 scores to a significant extent, although with placebo, there were significant (p = 0.002) reductions in the mean OSDI symptom subscale score (from 21.4 to 16.2) and the mean OSDI total score (from 22.5 to 17.7).[31]
- In the Japanese trial, the global usefulness of cevimeline 30 mg three times daily was rated significantly higher than that of placebo (43% vs 21%; p = 0.006).[30]

Long-Term Follow-Up

Two 52-week open-label studies conducted in the US[29] and Japan[32] examined the efficacy of cevimeline in the longer term. Only interim data from the US study (obtained from the FDA review document[29]) are available.

Some patients with Sjögren's syndrome who were enrolled in the open-label, multicentre, flexible-dose, 52-week US study had participated in previous phase II or III studies, whereas others had not previously received cevimeline.[29] Patients (n = 362) could receive oral cevimeline 15, 30 or 60 mg three times daily depending on response. Mean patient age was 54.2 years and 95% of participants were female.[29]

- Increased salivary flow was maintained in the longer term with cevimeline in patients with Sjögren's syndrome and dry mouth.[29] At the final visit, the change in salivary flow from predose to postdose was 0.131, 0.134 and 0.160 mL/min with cevimeline 15, 30 and 60 mg three times daily.
- By week 20, 88% of patients were satisfied with their cevimeline dosage; satisfaction rates ranged from 90% to 96% for the remainder of the trial.[29] Similar results were seen for investigators with 88% of investigators satisfied with the dosage prescribed at week 20; investigator satisfaction rates were 90–96% for the rest of the trial.

4. Tolerability

Data concerning the tolerability of oral cevimeline in patients with Sjögren's syndrome were obtained from 6-[27] and 12-week[28] randomized, double-blind, multicentre trials conducted in the US (n = 197[28] and 75[27]) and from an open-label, multicentre, flexible-dose, 52-week US study (n = 362)[29] [see section 3 for study details].

Comparisons with Placebo

- Oral cevimeline 30 mg three times daily was generally well tolerated in patients with Sjögren's syndrome; many of the most frequently reported adverse events (e.g. nausea, increased sweating, rhinitis, diarrhoea) reflected the pharmacological action of cevimeline (i.e. muscarinic agonism).[21,27,28]
- In the 12-week trial, drug-related adverse events occurred in 48.4% of patients receiving cevimeline 30 mg three times daily and in 25.7% of patients receiving placebo. The most commonly occurring adverse events included nausea, headache, increased sweating, diarrhoea, sinusitis and pharyngitis; only nausea and increased sweating occurred in significantly more patients receiving cevimeline 30 mg three times daily than placebo (figure 1).[28]
- Serious adverse events occurred in 1.6% of cevimeline 30 mg three times daily recipients and 2.9% of placebo recipients.[28] Study withdrawal because of adverse events occurred in 16.1% of patients receiving cevimeline 30 mg three times daily and 4.3% of patients receiving placebo.[28]
- A similar adverse event profile was seen in the 6-week trial, although there was no significant difference between patients receiving cevimeline 30 mg three times daily and those receiving placebo in the incidence of any adverse events.[27]
- In general, no significant changes in laboratory parameters[27,28] or vital signs[27] were seen in patients receiving cevimeline 30 mg three times daily.

Long-Term Follow-Up

- Oral cevimeline was generally well tolerated in patients with Sjögren's syndrome in the open-label, multicentre, flexible-dose, 52-week US study.[29]

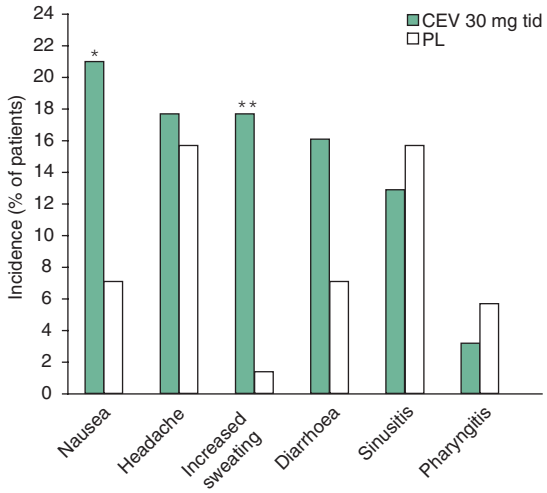


Fig. 1. Tolerability of oral cevimeline (CEV) in patients with Sjögren's syndrome. Incidence of adverse events in a randomized, double-blind, multicentre trial in which patients received oral CEV 30 mg three times daily (tid) [n = 62] or placebo (PL) [n = 70] for 12 wk. This trial also contained a treatment arm in which patients received CEV 15 mg tid (n = 65); however, results from this treatment arm are not shown. * p = 0.02, ** p = 0.001 vs PL.

Adverse events were reported in 61.8%, 76.2% and 79.8% of patients who received cevimeline 15, 30 or 60 mg three times daily, with 5.0%, 1.9% and 6.1% of patients in the corresponding treatment groups discontinuing therapy because of adverse events.

- Among patients receiving cevimeline 15, 30 or 60 mg three times daily, the most commonly reported adverse events were increased sweating (5.2%, 19.3% and 38.4% of patients), nausea (9.9%, 13.6% and 14.6%), sinusitis (8.2%, 11.3% and 7.9%), diarrhoea (10.2%, 9.8% and 6.1%), headache (11.0%, 11.0% and 4.2%) and upper respiratory tract infection (6.9%, 11.3% and 3.6%).[29]
- Serious adverse events were reported in 2.2% of patients receiving cevimeline 15 mg three times daily, 2.5% of patients receiving cevimeline 30 mg three times daily and 6.1% of patients receiving cevimeline 60 mg three times daily.[29]

5. Dosage and Administration

The recommended dosage of oral cevimeline (administered as capsules) for the treatment of symptoms of dry mouth in patients with Sjögren's syndrome patients is 30 mg three times daily.[21] Local prescribing information should be consulted for information regarding contraindications, warnings and precautions.

6. Cevimeline: Current Status

Cevimeline is available in several countries (including Japan, Taiwan and the US) for the treatment of symptoms of dry mouth in patients with Sjögren's syndrome.

In well designed placebo-controlled trials in patients with Sjögren's syndrome, oral cevimeline 30 mg three times daily significantly improved symptoms of dry mouth and the salivary flow rate. Increased salivary flow was also maintained in the longer term. Cevimeline was generally well tolerated in patients with Sjögren's syndrome with many of the most frequently reported adverse events reflecting the pharmacological action of the drug.

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