FORTICAL® (calcitonin-salmon [rDNA origin]) Nasal Spray for intranasal use Rx only

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FORTICAL® safely and effectively. See full prescribing information for FORTICAL.

FORTICAL® (calcitonin-salmon [rDNA origin]) Nasal Spray for intranasal use
Initial U.S. Approval: 2005

---RECENT MAJOR CHANGES---
Indications and Usage (1.2) 07/2014
Warnings and Precautions (5.2, 5.4) 07/2014

----INDICATIONS AND USAGE-----
Fortical is a calcitonin indicated for the treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause when alternative treatments are not suitable. Fracture reduction efficacy has not been demonstrated (1.1).

Limitations of Use:
- Due to the possible association between malignancy and calcitonin-salmon use, the need for continued therapy should be re-evaluated on a periodic basis (1.2, 5.4).
- Calcitonin-salmon nasal spray has not been shown to increase bone mineral density in early postmenopausal women (1.2).

---DOSAGE AND ADMINISTRATION---
For intranasal use only: one spray (200 International Units) per day, alternating nostrils daily (2.1).
- Prior to first use, allow the bottle to reach room temperature and prime the pump (2.2).
- Ensure adequate calcium and Vitamin D intake. (2.3)

---DOSAGE FORMS AND STRENGTHS---
Nasal spray: 2200 International Units per mL of calcitonin-salmon in a 3.7 mL fill glass bottle with screw-on pump. Each actuation delivers 200 International Units of calcitonin-salmon. (3)

---CONTRAINDICATIONS---
- Hypersensitivity to calcitonin-salmon or any of the excipients (4)

---WARNINGS AND PRECAUTIONS---
- Serious hypersensitivity reactions, including anaphylactic shock have been reported. Consider skin testing prior to treatment in patients with suspected hypersensitivity to calcitonin-salmon. (5.1)
- Hypocalcemia has been reported. Ensure adequate intake of calcium and vitamin D (5.2).
- Nasal adverse reactions including severe ulceration can occur. Periodic nasal examinations are recommended (5.3).
- Malignancy: A meta-analysis of 21 clinical trials suggests an increased risk of overall malignancies in calcitonin-salmon treated patients (5.4.6.1)
- Circulating antibodies to calcitonin-salmon may develop, and may cause loss of response to treatment (5.5)

---ADVERSE REACTIONS---
The most common adverse reactions (3% or greater) are rhinitis, epistaxis and other nasal symptoms, back pain, arthralgia, and headache. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Upsher-Smith Laboratories, Inc. at 1-855-899-9180 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---DRUG INTERACTIONS---
- Concomitant use of calcitonin-salmon and lithium may lead to a reduction in plasma lithium concentrations due to increased urinary clearance of lithium. The dose of lithium may require adjustment. (7)

---USE IN SPECIFIC POPULATIONS---
- There are no data to support use in children (8.4).
- Nasal reactions are more common in elderly patients. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Treatment of Postmenopausal Osteoporosis
FORTICAL nasal spray is indicated for the treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause. Fracture reduction efficacy has not been demonstrated. FORTICAL nasal spray should be reserved for patients for whom alternative treatments are not suitable (e.g., patients for whom other therapies are contraindicated or for patients who are intolerant or unwilling to use other therapies).

1.2 Important Limitations of Use
- Due to the possible association between malignancy and calcitonin-salmon use, the need for continued therapy should be re-evaluated on a periodic basis [see Warnings and Precautions (5.4)].
- Calcitonin-salmon nasal spray has not been shown to increase spinal bone mineral density in early postmenopausal women.

2 DOSAGE AND ADMINISTRATION
2.1 Basic Dosing Information
The recommended dose of FORTICAL nasal spray is 1 spray (200 International Units) per day intranasally, alternating nostrils daily.

2.2 Priming (Activation) of Pump
Unopened FORTICAL nasal spray should be stored in the refrigerator. Before using the first dose of FORTICAL nasal spray, the patient should wait until the bottle has reached room temperature. Remove the protective cap and clip from the actuator of FORTICAL nasal spray. To prime the pump before it is used for the first time, the bottle should be held upright and the two white side arms of the pump depressed toward the bottle at least 5 times until a full spray is produced. The pump is primed once the first full spray is emitted. To administer, the nozzle should be carefully placed into the nostril with the patient's head in the upright position, then the pump should be firmly depressed toward the bottle. The pump should not be primed before each daily use.

2.3 Recommendations for Calcium and Vitamin D Supplementation
Patients who use FORTICAL nasal spray should receive adequate calcium (at least 1000 mg elemental calcium per day) and Vitamin D (at least 400 International Units per day).

3 DOSAGE FORMS AND STRENGTHS
FORTICAL nasal spray consists of one glass bottle and one screw-on pump. The bottle contains 3.7 mL of calcitonin-salmon clear solution at a concentration of 2200 International Units per mL. A primed pump delivers 0.09 mL (200 International Units) calcitonin-salmon per actuation.

4 CONTRAINDICATIONS
Hypersensitivity to calcitonin-salmon or any of the excipients. Reactions have included anaphylactic shock, anaphylaxis, bronchospasm, and swelling of the tongue or throat [see Warnings and Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
Serious hypersensitivity reactions have been reported in patients receiving calcitonin-salmon nasal spray, e.g., bronchospasm, swelling of the tongue or throat, anaphylaxis and anaphylactic shock. Reports of serious hypersensitivity reactions with injectable calcitonin-salmon have also been reported, including reports of death attributed to anaphylaxis. The usual provisions should be made for emergency treatment if such a reaction occurs. Hypersensitivity reactions should be differentiated from generalized flushing and hypotension [see Contraindications (4)].

5.2 Hypocalcemia
For patients with suspected hypersensitivity to calcitonin-salmon, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of a calcitonin-salmon injectable product. Healthcare providers may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from Upsher-Smith Laboratories, Inc. by calling toll-free at 1-888-650-3789.

5.3 Hypercalcemia
Hypocalcemia associated with tetany (i.e. muscle cramps, twitching) and seizure activity has been reported with calcitonin therapy. Hypocalcemia must be corrected before initiating therapy with FORTICAL nasal spray. Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FORTICAL nasal spray. Use of FORTICAL nasal spray is recommended in conjunction with an adequate intake of calcium and vitamin D [see Dosage and Administration (2.3)].

8 USE IN SPECIFIC POPULATIONS
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8.3 Nursing Mothers
8.4 Pediatric Use
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*Sections or subsections omitted from the full prescribing information are not listed.
5.3 Nasal Adverse Reactions

Adverse reactions related to the nose including rhinitis and epistaxis have been reported. Development of mucosal alterations may occur. Therefore, periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum and mucosal blood vessels are recommended prior to start of treatment with Fortical nasal spray, periodically during the course of therapy, and at any time nasal symptoms occur.

Fortical nasal spray should be discontinued if severe ulceration of the nasal mucosa occurs, as indicated by ulcers greater than 1.5 mm in diameter or penetrating below the mucosa, or those associated with heavy bleeding. Although smaller ulcers often heal without withdrawal of Fortical nasal spray, medication should be discontinued temporarily until healing occurs [see Adverse Reactions (6.1)].

5.4 Malignancy

In a meta-analysis of 21 randomized, controlled clinical trials with calcitonin-salmon (nasal spray or investigational oral formulations), the overall incidence of malignancies reported was higher among calcitonin-salmon-treated patients (4.1%) compared with placebo-treated patients (2.9%). This suggests an increased risk of malignancies in calcitonin-salmon-treated patients compared to placebo-treated patients. The benefits for the individual patient should be carefully considered against possible risks [see Adverse Reactions (6.1)].

5.5 Antibody Formation

Circulating antibodies to calcitonin-salmon have been reported with calcitonin-salmon nasal spray. The possibility of antibody formation should be considered in any patient with an initial response to Fortical nasal spray who later stops responding to treatment [see Adverse Reactions (6.3)].

5.6 Urine Sediment Abnormalities

Coarse granular casts and casts containing renal tubular epithelial cells were reported in young adult volunteers at bed rest who were given injectable calcitonin-salmon to study the effect of immobilization on osteoporosis. There was no other evidence of renal abnormality and the urine sediment normalized after calcitonin-salmon was stopped. Periodic examinations of urine sediment should be considered. Urine sediment abnormalities have not been reported in ambulatory volunteers treated with calcitonin-salmon nasal spray.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Hypersensitivity Reactions, including anaphylaxis [see Warnings and Precautions (5.1)]
- Hypocalcemia [see Warnings and Precautions (5.2)]
- Nasal Adverse Reactions [see Warnings and Precautions (5.3)]
- Malignancy [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of calcitonin-salmon nasal spray in the treatment of postmenopausal osteoporosis was assessed in 5 randomized, double-blind, placebo controlled trials that enrolled postmenopausal women, aged 45-75 years. The duration of the trials ranged from 1 to 2 years. The incidence of adverse reactions reported in studies involving postmenopausal osteoporotic patients chronically exposed to calcitonin-salmon nasal spray (N=341) and to placebo nasal spray (N=131), and reported in greater than 3% of calcitonin-salmon treated patients are presented in the following table. Other than flushing, nausea, possible allergic reactions, and possible local irritative effects in the respiratory tract, a relationship to calcitonin-salmon nasal spray has not been established.

Table 1: Adverse Reactions Occurring in At Least 3% of Postmenopausal Patients Treated Chronically

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Calcitonin-Salmon Nasal Spray</th>
<th>Placebo Nasal Spray</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=341 % of Patients</td>
<td>N=131 % of Patients</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Symptom of Nose†</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Back Pain</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

†Symptom of nose includes: nasal crusts, dryness, redness or erythema, nasal sores, irritation, itching, thick feeling, soreness, pallor, infection, stenosis, runny/blocked, small wound, bleeding wound, tenderness, uncomfortable feeling and sore across bridge of nose.

Table 2: Risk Difference for Malignancies in Calcitonin-Salmon-Treated Patients Compared with Placebo-Treated Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Malignancies</th>
<th>Risk Difference¹ (%)</th>
<th>95% Confidence Interval² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (nasal spray + oral)</td>
<td>All</td>
<td>1.0</td>
<td>(0.3, 1.6)</td>
</tr>
<tr>
<td>All (nasal spray + oral)</td>
<td>Excluding basal cell carcinoma</td>
<td>0.5</td>
<td>(-0.1, 1.2)</td>
</tr>
<tr>
<td>All (nasal spray only)</td>
<td>All</td>
<td>1.4</td>
<td>(0.3, 2.6)</td>
</tr>
<tr>
<td>All (nasal spray only)</td>
<td>Excluding basal cell carcinoma</td>
<td>0.8</td>
<td>(-0.2, 1.8)</td>
</tr>
</tbody>
</table>

¹ The overall adjusted risk difference is the difference between the percentage of patients who had any malignancy (or malignancy excluding basal cell carcinoma) in calcitonin-salmon and placebo treatment groups, using the Mantel-Haenszel (MH) fixed-effect method. A risk difference of 0 is suggestive of no difference in malignancy risks between the treatment groups.

² The corresponding 95% confidence interval for the overall adjusted risk difference also based on MH fixed-effect method.

6.2 Postmarketing Experience

Because postmarketing adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been reported during post-approval use of calcitonin-salmon nasal spray.

- **Allergic / Hypersensitivity Reactions**: Serious allergic reactions have been reported in patients receiving calcitonin-salmon nasal spray, including anaphylaxis and anaphylactic shock.

- **Hypocalcemia**: Hypocalcemia with paresthesia has been reported.

- **Body as a whole**: Facial or peripheral edema

- **Cardiovascular**: Hypertension, vasodilatation, syncope, chest pain

- **Nervous system**: Dizziness, seizure, visual or hearing impairment, tinnitus

- **Respiratory/ Special Senses**: Cough, bronchospasm, dyspnea, loss of taste/smell

- **Skin**: Rash, dermatitis, pruritus, alopecia, increased sweating

- **Gastrointestinal**: Diarrhea

- **Nervous system disorders**: Tremor
6.3 Immunogenicity
Consistent with the potentially immunogenic properties of medicinal products containing peptides, administration of Fortical may trigger the development of anti-calcitonin antibodies. In a two-year calcitonin-salmon nasal spray clinical study that evaluated immunogenicity, a measurable antibody titer was found in 69% of patients treated with calcitonin-salmon and 3% of placebo-treated patients. Antibody formation may be associated with a loss of response to treatment [see Warnings and Precautions (5.5)].

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of a positive antibody test result may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of antibodies to calcitonin-salmon nasal spray with the incidence of antibodies to other calcitonin-containing products may be misleading.

7 DRUG INTERACTIONS
No formal drug interaction studies have been performed with calcitonin-salmon nasal spray.

Concomitant use of calcitonin-salmon and lithium may lead to a reduction in plasma lithium concentrations due to increased urinary clearance of lithium. The dose of lithium may require adjustment.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C:
Risk Summary
There are no adequate and well-controlled studies in pregnant women. Fortical nasal spray should be used during pregnancy only if the potential benefit justifies the use as compared with potential risks to the patient and fetus. Based on animal data, Fortical is predicted to have low probability of increasing the risk of adverse developmental outcomes above background risk.

Animal Data
Synthetic calcitonin-salmon has been shown to cause a decrease in fetal birth weights in rabbits when given by subcutaneous injection at doses 70-278 times the intranasal dose recommended for human use based on body surface area. No embryo/fetal toxicities related to synthetic calcitonin-salmon were reported from maternal subcutaneous daily doses in rats up to 80 International Units/kg/day from gestation day 6 to 15.

8.3 Nursing Mothers
It is not known whether this drug is excreted in human milk. No studies have been conducted to assess the impact of Fortical on milk production in humans, its presence in human breast milk, or its effects on the breast-fed child. Because many drugs are excreted in human milk, caution should be exercised when Fortical is administered to a nursing woman. Synthetic calcitonin-salmon has been shown to inhibit lactation in rats.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use
In a multi-centered, double-blind, randomized clinical study of calcitonin-salmon nasal spray, 279 patients were less than 65 years old, while 467 patients were 65 to 74 years old and 196 patients were 75 and over. Compared to subjects less than 65 years old, the incidence of nasal adverse reactions (rhinitis, irritation, erythema, and excoriation) was higher in patients over the age of 65, particularly those over the age of 75. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE
The pharmacologic actions of Fortical nasal spray suggest that hypocalcemic tetany could occur in overdose. Therefore, provisions for parenteral administration of calcium should be available for the treatment of overdose.

Single doses of calcitonin-salmon nasal spray up to 1600 International Units, doses up to 800 International Units per day for 3 days and chronic administration of doses up to 600 International Units per day have been studied without serious adverse effects.

11 DESCRIPTION
Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland in mammals and by the ultimobranchial gland of birds and fish. The active ingredient in Fortical (calcitonin-salmon [rDNA origin]) nasal spray is a polypeptide of 32 amino acids manufactured by recombinant DNA technology and is identical to calcitonin-salmon produced by chemical synthesis.
drug appear approximately 10 minutes after nasal administration. The terminal half-life \((t_{1/2})\) of calcitonin-salmon is calculated to be about 23 minutes. There is no accumulation of the drug on repeated nasal administration at 10 hour intervals for up to 15 days. Absorption of Fortical nasal spray has not been studied in postmenopausal women.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenicity**

The incidence of pituitary adenomas was increased in rats after one and two years of subcutaneous exposure to synthetic calcitonin-salmon. The significance of this finding to humans is unknown because pituitary adenomas are very common in rats as they age, the pituitary adenomas did not transform into metastatic tumors, there were no other clear treatment-related neoplasms, and synthetic calcitonin-salmon related neoplasms were not observed in mice after two years of dosing.

**Rat findings:**

The only clear neoplastic finding in rats dosed subcutaneously with synthetic calcitonin-salmon was an increase in the incidence of pituitary adenomas in male Fisher 344 rats and female Sprague Dawley rats after one year of dosing and male Sprague Dawley rats dosed for one and two years. In female Sprague Dawley rats, the incidence of pituitary adenomas after two years was high in all treatment groups (between 80% and 92% including the control groups) such that a treatment-related effect could not be distinguished from natural background incidence. The lowest dose in male Sprague Dawley rats that developed an increased incidence of pituitary adenomas after two years of dosing (1.7 International Units/kg/day) is approximately 2 times the maximum recommended intranasal dose in humans (200 International Units/day) based on body surface area conversion between rats and humans and a 20-fold conversion factor to account for decreased clinical exposure via the intranasal route. The findings suggest that calcitonin-salmon reduced the latency period for development of non-functioning pituitary adenomas.

**Mouse findings:**

No carcinogenicity potential was evident in male or female mice dosed subcutaneously for two years with synthetic calcitonin-salmon at doses up to 800 International Units/kg/day. The 800 International Units/kg/day dose is approximately 390 times the maximum recommended intranasal dose in humans (200 International Units) based on scaling for body surface area and a 20-fold conversion factor to account for low clinical exposure via the intranasal route.

**Mutagenesis**

Synthetic calcitonin-salmon tested negative for mutagenicity using *Salmonella typhimurium* (5 strains) and *Escherichia coli* (2 strains), with and without rat liver metabolic activation, and was not clastogenic in a chromosome aberration test in Chinese Hamster V79 cells. There was no evidence that calcitonin-salmon was clastogenic in the in vivo mouse micronucleus test.

**Fertility**

Effects of calcitonin-salmon on fertility have not been assessed in animals.

### 14 CLINICAL STUDIES

Two randomized, placebo-controlled, two-year trials were conducted in 266 postmenopausal women who were greater than 5 years postmenopause with spinal, forearm or femoral bone mineral density (BMD) at least one standard deviation below the normal value for healthy premenopausal women (T-score < -1). In both studies, a total of 144 patients received calcitonin-salmon nasal spray 200 International Units or placebo daily. The intent-to-treat population comprised 139 patients who had at least one follow-up BMD measurement. In study 1, patients also received 500 mg daily calcium supplements, while in study 2, patients received no calcium supplementation. The primary endpoint for both studies was percent change in lumbar spine BMD at 2 years. Calcitonin-salmon nasal spray increased lumbar vertebral BMD relative to placebo in women with low bone mass who were greater than 5 years post menopause (see Table 3 below).

<table>
<thead>
<tr>
<th>Study</th>
<th>Lumbar Spine Bone Mineral Density, Mean Change From Baseline (in %) at Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study 1 (with calcium supplement) Study 2 (no calcium supplement)</td>
</tr>
<tr>
<td></td>
<td>n (ITT) = 100 n (ITT) = 39</td>
</tr>
<tr>
<td>Calciton-salmon 200 IU NS daily</td>
<td>+1.56 +0.20</td>
</tr>
<tr>
<td>Placebo</td>
<td>+1.02 -1.85</td>
</tr>
<tr>
<td>Treatment Difference</td>
<td>+1.36 +2.87</td>
</tr>
<tr>
<td>p-value†</td>
<td>&lt; 0.05 &lt; 0.005</td>
</tr>
</tbody>
</table>

**ITT: Intent To Treat**

**IU: International Units**

**NS: nasal spray**

*p-values by parametric testing (2-tailed 2-sample t-test)*

No effects of calcitonin-salmon nasal spray on cortical bone of the forearm or hip were demonstrated.

In clinical studies of postmenopausal osteoporosis, bone biopsy and radial bone mass assessments at baseline and after 26 months of daily injectable calcitonin-salmon indicate that calcitonin therapy results in the formation of normal bone.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### How Supplied

Fortical® (calcitonin-salmon [rDNA origin]) nasal spray is presented as a metered dose solution in a 3.7 mL fill amber glass bottle with screw-on pump that contains 2200 International Units of calcitonin-salmon per mL. Following priming, the pump will deliver 200 International Units of calcitonin-salmon per activation (0.09 mL per spray). Fortical® nasal spray is provided in individual boxes containing one glass bottle with screw cap and one screw-on pump (NDC# 0245-0008-35).

**Storage and Handling**

Store unopened bottle in refrigerator between 2° to 8°C (36° to 46°F). Protect from freezing. After opening, store bottle in use in an upright position at 20° to 25°C (68° to 77°F). Excursions permitted to 15° to 30°C (59° to 86°F). Discard the bottle after 30 doses have been used.

### 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use).

- Instruct patients on pump assembly, priming of the pump, and nasal introduction of Fortical nasal spray. Although instructions for patients are supplied with the individual bottle, procedures for use should be demonstrated to each patient [see Dosage and Administration (2.2)]. Patients should notify their healthcare provider if they develop significant nasal irritation [see Warnings and Precautions (5.3)].
- Inform patients of the potential increase in risk of malignancy [see Warnings and Precautions (5.4)].
- Advise patients to maintain an adequate calcium (at least 1000 mg elemental calcium per day) and vitamin D (at least 400 International Units per day) intake [see Dosage and Administration (2.3)].
- Instruct patients to seek emergency medical help or go to the nearest hospital emergency room right away if they develop any signs or symptoms of a serious allergic reaction.
- Advise patients how to correctly store unopened and opened product [see How Supplied/Storage and Handling (16)]. Advise patients that the bottle should be discarded after 30 doses, because after 30 doses, each spray may not deliver the correct amount of medication even if the bottle is not completely empty.

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