For the use of Registered Ophthalmologists only.

Ranibizumab

RanizuRel™

Solution for intravitreal injection

GENERIC NAME

Ranibizumab

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 mg vial contains Ranibizumab 2.3 mg, L-histidine 10 mM, α,α-trehalose dihydrate (10%), Polysorbate 20 (0.01%) and Water for Injection QS at pH 5.5.

Each 0.3 mg vial contains Ranibizumab 1.38 mg, L-histidine 10 mM, α,α-trehalose dihydrate (10%), Polysorbate 20 (0.01%) and Water for Injection QS at pH 5.5.

DOSAGE FORM AND STRENGTH

0.5 mg vial containing 2.3 mg in 0.23 mL (10 mg/mL solution)

0.3 mg vial containing 1.38 mg in 0.23 mL (6 mg/mL solution)

CLINICAL PARTICULARS

Therapeutic indications

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)
- Myopic Choroidal Neovascularization (mCNV)

Posology and method of administration

General Dosing Information:

FOR OPHTHALMIC INTRAVITREAL INJECTION

- **Neovascular (Wet) Age-Related Macular Degeneration (AMD)**

RanizuRel™ (Ranibizumab) 0.5 mg (0.05 mL of 10 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days). Although not as effective, patients may be treated with 3 monthly doses followed by less frequent dosing with regular assessment. In the 9 months after three initial monthly doses, less frequent dosing with 4-5 doses on average is expected to maintain visual acuity while monthly dosing may be expected to result in an additional average 1-2 letter gain. Patients should be assessed regularly. Although not as effective, patients may also be treated with one dose every 3 months after 4 monthly doses. Compared with continued monthly dosing, dosing every 3 months over the next 9 months will lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average. Patients should be assessed regularly.

- **Macular Edema Following Retinal Vein Occlusion (RVO)**

RanizuRel™ (Ranibizumab) 0.5 mg (0.05 mL of 10 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

In innovator studies, patients received monthly injections of ranibizumab for 6 months. In spite of being guided by optical coherence tomography and visual acuity re-treatment criteria, patients who were then not treated at month 6 experienced on average, a loss of visual acuity at month 7, whereas patients who were treated at month 6 did not. Patients should be treated monthly.

- **Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)**

RanizuRel™ (Ranibizumab) 0.3 mg (0.05 mL of 6 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

- **Myopic Choroidal Neovascularization (mCNV)**

RanizuRel™ (Ranibizumab) 0.5 mg (0.05 mL of 10 mg/mL solution) is recommended to be initially administered by intravitreal injection once a month (approximately 28 days) for up to 3 months. Patients may be retreated if needed.

Preparation for administration:

The intravitreal injection procedure should be carried out under controlled aseptic conditions. Adequate anaesthesia and a broad-spectrum microbicide should be given prior to the injection. Prior to and 30 minutes following the intravitreal injection, patients should be monitored for elevation in intraocular pressure using tonometry. Monitoring may also consist of a check for perfusion of the optic nerve head immediately after the injection. Patients should also be monitored for and instructed to report any symptoms suggestive of endophthalmitis without delay following the injection. Each vial should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile conditions should be changed before RanizuRel™ (Ranibizumab) is administered to the other eye. No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

Method of administration:

Use aseptic technique to carry out the following preparation steps:

1. Prepare for intravitreal injection with the following devices for single use:
   - a 5-micron sterile filter needle (18-gauge x 1½ inch)
   - a 1 mL sterile syringe (with marking to measure 0.05 mL)
   - a sterile injection needle (30-gauge x ½ inch)
2. Before withdrawal, bring the product to room temperature, remove the cap and disinfect the outer part of the rubber stopper of the vial.
3. Place a 5-micron filter needle (18-gauge x 1½ inch) onto a 1 mL syringe using aseptic technique.
4. Push the filter needle into the center of the vial stopper until the needle touches the bottom edge of the vial.
5. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.
6. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
7. The filter needle should be discarded after withdrawal of the vial contents and must not be used for the intravitreal injection.
8. Attach a 30-gauge x 1/2-inch sterile injection needle firmly onto the syringe by screwing it tightly. Carefully remove the needle cap by pulling it straight off. Do not wipe the needle at any time.
9. Hold the syringe with the needle pointing up. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top.
10. Hold the syringe at eye level, and carefully push the plunger rod until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

In adults the injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 mL is then delivered; a different scleral site should be used for subsequent injections.

Contraindications:

- **Ocular or Periocular Infections**

Ranibizumab is contraindicated in patients with ocular or periocular infections.

- **Hypersensitivity**

Ranibizumab is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in the preparation. Hypersensitivity reactions may manifest as severe intraocular inflammation.

Special warnings and precautions for use:

- **Endophthalmitis and Retinal Detachments**

Intravitreal injections, including those with ranibizumab, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering ranibizumab. In addition, patients should be monitored following the injection to permit early treatment should an infection occur.

- **Increases in Intraocular Pressure**

Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with ranibizumab. Monitor intraocular pressure prior to and following intravitreal injection with ranibizumab and manage appropriately.

- **Thromboembolic Events**

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the innovator clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

- **Fatal Events in Patients with Diabetic Macular Edema and Diabetic Retinopathy at Baseline**

Diabetic Macular Edema and Diabetic Retinopathy

Although the rate of fatal events according to innovator data was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

Drug interactions:

Drug interaction studies have not been conducted with RanizuRel™ (Ranibizumab).

Ranibizumab intravitreal injection has been used adjunctively with photodynamic therapy (PDT). Patients with neovascular AMD developed serious intraocular inflammation in innovator studies and mostly occurred when ranibizumab was administered 7 days (± 2 days) after PDT.

Use in special populations:

- **Pregnancy**

There are no adequate and well-controlled studies of ranibizumab administration in pregnant women. Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with ranibizumab may pose a risk to human embryo-fetal development. Ranibizumab should be given to a pregnant woman only if clearly needed.

- **Lactation**

There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when ranibizumab is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ranibizumab and any potential adverse effects on the breastfed child from ranibizumab.

- **Females and Males of Reproductive Potential**

No studies on the effects of ranibizumab on fertility have been conducted and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, it may pose a risk to reproductive capacity.

- **Pediatric Use**

The long-term safety profile in preterm infants and pediatrics has not been established.

- **Geriatric Use**

In the innovator clinical studies, no notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

Effects on ability to drive and use machines:

The treatment procedure may induce temporary visual disturbances, which may affect the ability to drive or use machines. Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.

Undesirable effects:

The majority of adverse reactions reported following administration of ranibizumab are related to the intravitreal injection procedure. The most frequently reported ocular adverse reactions following injection of ranibizumab are: eye pain, ocular hyperaemia, increased intraocular pressure, vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, increased lacrimation, blepharitis, dry eye and eye pruritus. The most frequently reported non-ocular adverse reactions are headache, nasopharyngitis and arthralgia. Less frequently reported, but more serious, adverse reactions include endophthalmitis, blindness, retinal detachment, retinal tear and iatrogenic traumatic cataract. The adverse reactions experienced following administration of ranibizumab in innovator clinical trials are summarised in the table below.

In the following table 1, adverse reactions are listed by system organ class and frequency using the following convention: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse events by system organ class.

Infections and infestations	
Very common	Nasopharyngitis
Common	Urinary tract infection*
Blood and lymphatic system disorders	
Common	Anaemia
Immune system disorders	
Common	Hypersensitivity
Psychiatric disorders	
Common	Anxiety
Nervous system disorders	
Very common	Headache
Eye disorders	
Very common	Vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperaemia, eye pruritus.
Common	Retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous haemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctuate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site haemorrhage, eye haemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid oedema, eyelid pain, conjunctival hyperaemia.
Uncommon	Blindness, endophthalmitis, hypopyon, hyphaema, keratopathy, iris adhesion, corneal deposits, corneal oedema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation.
Respiratory, thoracic and mediastinal disorders	
Common	Cough
Gastrointestinal disorders	
Common	Nausea
Skin and subcutaneous tissue disorders	
Common	Allergic reactions (rash, urticaria, pruritus, erythema)
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Investigations	
Very common	Intraocular pressure increased
* observed only in DME population	

In the phase III comparative study of RanizuRel™ (Ranibizumab), a total of 38 adverse events were reported out of which 26 were reported in the RanizuRel™ (Ranibizumab) or test arm and 12 were reported in the innovator or comparator arm. There were 16 (15.09%) subjects in test arm and 05 (9.43%) subjects in the comparator arm with at least one treatment emergent adverse event. There were 05 (4.72%) subjects in test arm and 01 (1.89%) subjects in the comparator arm with at least one TEAE related to study medication. According to SOC (System Organ Class) in the test arm, the most commonly reported (incidence ≥ 5%) TEAEs were related to eye disorders 11 (8.49%). Other TEAEs were related to nervous system disorders 3(2.83%), general disorders and administration site conditions 3 (2.83%), gastrointestinal disorders 1 (0.94%), immune system disorders 1 (0.94%), infections and infestation disorders 2 (1.89%) and respiratory, thoracic and mediastinal disorders 1 (0.94%). In the comparator arm, the most commonly reported (incidence ≥ 5%) TEAEs were related to eye disorders 08 (7.55%). Other TEAEs were related to Ear and Labyrinth disorders. In test arm, adverse events related to eye disorders included conjunctival hyperaemia, eye discharge, eye haemorrhage, macular fibrosis, eye pain, vitreous floaters, and vitreous haze while in comparator arm, adverse events related to eye disorders were conjunctival hyperaemia, cystoid macular oedema, macular oedema and ocular hyperaemia. Summary of treatment emergent adverse events by system organ class and preferred term (Safety population) is presented in Table 2.

Table 2: Summary of treatment emergent adverse events by system organ class and preferred term (Safety population)

Body System	Preferred Term	RanizuRel™ (Ranibizumab) (N=106) n%E
Subjects with at least one Adverse Event		16 (15.09%) 26
Ear and labyrinth disorders		0 (0.00%)
	Otorrhoea	0 (0.00%)
Eye disorders		9 (8.49%) 13
	Conjunctival hyperaemia	1 (0.94%) 1
	Cystoid macular oedema	0 (0.00%)
	Eye discharge	1 (0.94%) 1
	Eye haemorrhage	1 (0.94%) 1
	Eye pain	4 (3.77%) 4
	Macular fibrosis	1 (0.94%) 1
	Macular oedema	1 (0.94%) 1
	Ocular hyperaemia	0 (0.00%)
	Vitreous floaters	2 (1.89%) 3
	Vitreous haze	1 (0.94%) 1
Gastrointestinal disorders		1 (0.94%) 1
	Diarrhoea	1 (0.94%) 1
General disorders and administration site conditions		3 (2.83%) 3
	Asthenia	1 (0.94%) 1
	Death	1 (0.94%) 1
	Pyrexia	1 (0.94%) 1
Immune system disorders		1 (0.94%) 1
	Drug hypersensitivity	1 (0.94%) 1
Infections and infestations		2 (1.89%) 2
	Conjunctival congestion	1 (0.94%) 1
	Conjunctivitis	1 (0.94%) 1
Investigations		1 (0.94%) 2
	Blood creatinine increased	1 (0.94%) 1
	Blood urea increased	1 (0.94%) 1
Nervous system disorders		3 (2.83%) 3
	Dizziness	1 (0.94%) 1
	Paraesthesia	1 (0.94%) 1
	Syncope	1 (0.94%) 1
Respiratory, thoracic and mediastinal disorders		1 (0.94%) 1
	Cough	1 (0.94%) 1

In this study, one death case was reported in RanizuRel™ (Ranibizumab) arm which was a known case of Ischemic heart disease (IHD) from previous 3 years and investigator assessed the causality as unlikely related with study drug. No other serious adverse events were reported during this study.

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 on toll free number 18001033900 or at rls.drugsafety@relbio.com.

Overdose:

Cases of accidental overdose have been reported from the innovator clinical studies in wet AMD and post-marketing data. Adverse reactions associated with these reported cases were intraocular pressure increased, transient blindness, reduced visual acuity, corneal oedema, corneal pain, and eye pain. If an overdose occurs, intraocular pressure should be monitored and treated, if deemed necessary by the attending physician. More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

PHARMACOLOGICAL PROPERTIES

Mechanism of Action:

Ranibizumab binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, $VEGF_{110}$. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

Pharmacodynamic properties:

Ranibizumab is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use. Ranibizumab is a VEGF-A antagonist that binds to and inhibits the biologic activity of active forms of human VEGF-A, including the cleaved form. VEGF-A has been shown to cause neovascularization (angiogenesis) and an increase in vascular permeability, which is thought to contribute to the progression of the neovascular form of age-related macular degeneration (AMD).

Clinical study:

A randomized, double-blind, parallel-group, comparative clinical study was done to evaluate efficacy, pharmacokinetics, safety and immunogenicity of RanizuRel™ (Ranibizumab) (test arm) with Innovator product (comparator arm) in patients with neovascular (wet) age-related macular degeneration. Total of 160 subjects were randomized (107 subjects in the test arm and 53 subjects in the comparator arm) and 159 subjects were with the study medication i.e. 106 subjects in the test arm and 53 subjects in the comparator arm. Eligible subjects were randomized to receive RanizuRel™ (Ranibizumab) or innovator product as per randomization schedule. Patients received ranibizumab 0.5 mg (0.05 mL of 10 mg/mL solution) as intravitreal injection once every 4 weeks for the treatment period of 24 weeks. The treatment period consisted of initial double blind-period of 16 weeks followed by open-label phase till week 24. The primary efficacy assessment was performed at week 16 based on the best corrected visual acuity as assessed with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, with the use of standardized refraction and testing protocol. In RanizuRel™ (Ranibizumab) or test arm, 104 (98.11%) patients lost fewer than 15 letters in visual acuity from baseline to week 16 compared to 53 (100%) patients in innovator or comparator arm. The difference in proportion of patients who lost fewer than 15 letters in visual acuity from baseline to week 16 was statistically not significant between the two treatment arms (p=0.314). At week 24, 105 (99.06%) patients in test arm lost fewer than 15 letters in visual acuity from baseline as compared to 53 (100%) patients in comparator arm. The difference in proportion of patients who lost fewer than 15 letters in visual acuity from baseline to week 24 (p=0.478) was statistically not significant between the two treatment arms. In test arm, 27 (25.47 %) patients gained at least 15 letters in visual acuity from baseline to week 16 compared to 17 (32.08%) patients in comparator arm. At week 24, 34 (32.08%) patients in test arm and 23 (43.30%) patients in comparator arm gained at least 15 letters in visual acuity from baseline. Difference in proportion of patients who gained at least 15 letters in visual acuity from baseline to week 16 (p=0.535) and week 24 (p=0.161) was statistically not significant between the two treatment arms. In test arm, the mean number of letter gain was 10.47 compared to 12.58 Letters in comparator arm at week 16. At week 24, the mean number of letter gain was 12.11 and 15.66 in test and comparator arms respectively. The difference in mean number of letter gain from baseline to week 16 (0.242) and week 24 (0.075) was statistically not significant between the two treatment arms. The median Snellen equivalent at baseline was 20/200 in both test and comparator arm and equivalent at week 16 was 20/100 in both arms and 20/80 in test arm compared to 20/100 comparator arm at week 24. There was no significant difference between the two arms for visual acuity Snellen equivalent of 20/40 or better and visual acuity Snellen equivalent of 20/200 or worse. In RanizuRel™ (Ranibizumab) arm, the mean change in central macular thickness was -77.79 μm compared to -70.35 μm in comparator arm at week 16. At week 24, the mean change in central macular thickness was -89.93 in test arm and -64.42 in comparator arm. Difference between the two treatment arms was statistically not significant at week 16 (p=0.550) and at week 24 (p=0.216).

Pharmacokinetic properties:

In the comparative phase III clinical study of RanizuRel™ (Ranibizumab), pharmacokinetic assessment in 24 subjects [12 from each group i.e., 1:1 ratio of RanizuRel™ (Ranibizumab) and comparator arms] was planned to be done to evaluate the systemic exposure to Ranibizumab. Given the intravitreal route of administration of ranibizumab, a limited absorption into the systemic circulation is expected. The results of innovator studies suggest that the predicted C_{max} is 1.7 ng/mL following 0.5 mg intravitreal injection of ranibizumab which is below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50%, 11-27 ng/mL, as assessed in an in vitro cellular proliferation assay. In addition, there are no indications that ranibizumab is accumulated in serum over time after monthly intravitreal treatment of 0.5 mg. Therefore, in view of the fairly low concentration of ranibizumab after intravitreal administration, any systemic pharmacological action is not expected. A limited absorption into the systemic circulation is expected, given the intravitreal route of administration of ranibizumab. The phase III study assay aimed at detecting serum ranibizumab concentration following 0.5 mg intravitreal injection of ranibizumab. However, the serum ranibizumab concentrations were too low to be detected with adequate sensitivity indicating limited systemic absorption of ranibizumab following intravitreal injection.

NON-CLINICAL PROPERTIES

Animal Toxicology or Pharmacology

Since ranibizumab is administered in eye, there is a low systemic exposure. Hence, animal studies have not been conducted to assess Carcinogenesis, Mutagenesis or Impairment of Fertility.

DESCRIPTION

RanizuRel™(Ranibizumab) is a recombinant humanized IgG1κ isotype monoclonal antibody fragment that selectively binds and inhibits the biological activity of human vascular endothelial growth factor A (VEGF-A). Ranibizumab lacks Fc region and has a molecular weight of 48 kilodaltons. The drug is produced in an *E.Coli* expression system.

The final product is sterile preservative free clear colourless to pale yellow solution in a single use vial. It is supplied as a kit along with one 5-micron sterile filter needle (18 G, 1 ½ inch), one 1 mL sterile syringe (with marking to measure 0.05 mL), a sterile injection needle (30G, ½ inch), one alcohol swab.

PHARMACEUTICAL PARTICULARS

Pharmaceutical form:

Solution for injection. Clear, colourless to pale yellow aqueous solution.

List of excipients:

- α,α-trehalose dihydrate
- L-histidine
- Water for Injection
- Polysorbate 20

Incompatibilities:

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf-life:

24 months from the date of manufacturing.

Packaging information:

0.5 mg single-use vial containing 2.3 mg in 0.23 mL or 0.3 mg single-use vial containing 1.38 mg in 0.23 mL along with one 5-micron sterile filter needle (18 G, 1 ½ inch), one 1 mL sterile syringe (with marking to measure 0.05 mL), a sterile injection needle (30G, ½ inch), one alcohol swab.

Storage and handing instructions:

Store in a refrigerator (2^0C - 8^0C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

PATIENT COUNSELLING INFORMATION

Advise patients that in the days following ranibizumab administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist.

DETAILS OF MANUFACTURER

Reliance Life Sciences Pvt. Ltd.
DALC, Plant 2 & 7, R-282, TTC area of MIDC, Thane Belapur Road, Rabale, Navi Mumbai - 400 701 INDIA.

DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Form CT 23: MF/BIO/20/000024 dated 30 Mar 2020

DATE OF REVISION

September 2023

Digitally signed by Guțan Ghenadie
Date: 2025.07.29 09:18:45 EEST
Reason: MoldSign Signature
Location: Moldova
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Reliance Life Sciences

Reliance Life Sciences Pvt. Ltd.

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