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PERSONALIZED MEDICINE

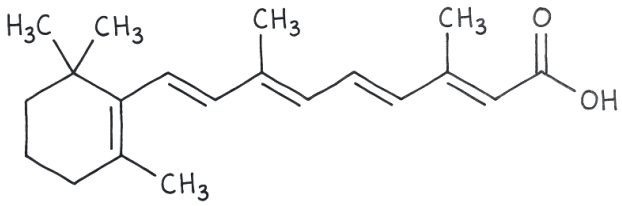
CLINICAL MONOGRAPH · DERMATOLOGY

Topical Tretinoin

Retinoid for acne, photo-aging, and select dermatologic conditions

Tretinoin is a vitamin A acid that you put on the skin. It has been a prescription dermatology medicine since 1971, originally as Retin-A for acne. Decades of use and many controlled trials show that tretinoin clears acne, smooths fine wrinkles, fades brown spots and melasma, and improves the overall look of sun-damaged skin [2].

It is sold under several brand names, Retin-A, Renova, Retin-A Micro, Atralin, Altreno, Avita, and as inexpensive generics. A compounded version from a 503A pharmacy is appropriate when a patient needs a strength that no manufacturer makes, a vehicle without a specific allergen, or a multi-ingredient cream like the classic 'Kligman formula' (tretinoin + hydroquinone + a low-strength steroid) for melasma, which has been the gold-standard pigmentation treatment for half a century [48116].



EVIDENCE POSTURE | FDA APPROVED | WELL STUDIED | REVIEWED **2026-05-11**

Pharmacist reviewed | Doctor led | Cold-chain ready | Patient choice preserved

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FOR CLINICIANS

Tretinoin is all-trans retinoic acid, the natural acid metabolite of vitamin A. It binds the retinoic acid receptors RARα, RARβ, and RARγ on keratinocytes and dermal fibroblasts, modulating transcription of genes that control epidermal proliferation, keratinocyte differentiation, follicular hyperkeratinization, melanogenesis, and dermal matrix turnover [3389]. FDA-approved indications across the product family include acne vulgaris (Retin-A 1971, Retin-A Micro, Avita, Atralin, Altreno) and the cutaneous signs of photoaging in the context of a comprehensive skin care and sun-avoidance program (Renova 1995) [393840]. Tri-Luma (fluocinolone 0.01% + hydroquinone 4% + tretinoin 0.05%) is FDA-approved for short-term moderate-to-severe melasma of the face [52 3537].

Pivotal photoaging evidence comes from the Kligman et al. 1986 open-label landmark in the Journal of the American Academy of Dermatology [1], the Weiss et al. 1988 double-blind vehicle-controlled trial in JAMA [2], the Ellis et al. 1990 long-term extension [3], and the Olsen et al. 1992 emollient-cream trial that supported the Renova approval [4]. Mechanistic work from the Voorhees and Fisher groups characterized UV-induced AP-1 activation, matrix metalloproteinase induction, and collagen degradation as the molecular substrate of photoaging, and demonstrated that pre-treatment with topical tretinoin blocks the UV induction of MMP-1, MMP-3, and MMP-9 and partially restores collagen synthesis in aged human skin [5047 10]. Acne evidence includes the Lucky et al [41]. 1998 double-blind multicenter trials of 0.025% cream and gel [1112], the AAD guidelines that designate topical retinoids as first-line therapy [3246], and the modern phase 3 program for the 0.05% polymeric-emulsion lotion (Altreno) across age, sex, and racial subgroups [484951]. Melasma evidence includes the Griffiths 1993 vehicle-controlled trial [7], the modified-Kligman protocols [14], and the pivotal Tri-Luma trials [1617]. Compounded use in 503A is the dominant pathway for custom strengths, allergen-free vehicles, and multi-ingredient melasma preparations that do not match an existing FDA-approved single product [31].

Why Personalized Topical Tretinoin

Tretinoin's FDA-approved strengths, 0.025%, 0.05%, and 0.1%, were calibrated against acne and photoaging trial cohorts and locked into a handful of fixed manufactured vehicles. Those numbers did not account for your skin's tolerance to retinoid dermatitis, your Fitzpatrick type and risk of post-inflammatory hyperpigmentation, whether you are treating melasma versus acne versus fine lines, the climate you live in, or the other actives already on your face. A patient who flushes through 0.025% in the first week and a patient who stalls out at 0.1% need different starting points, not the same three jars on the pharmacy shelf.

Compounding fills that gap. A 503A pharmacy can dispense intermediate strengths like 0.01% for a sensitive-skin start or 0.0125% and 0.075% for measured titration between the commercial steps, build the modified-Kligman melasma combinations (tretinoin plus hydroquinone plus a low-potency corticosteroid) that have been the gold-standard pigmentation regimen for decades but do not exist as a single off-the-shelf product outside Tri-Luma, pair tretinoin with niacinamide or azelaic acid for combination acne and pigmentation protocols, and swap the vehicle to an emollient cream, a lighter gel, or an allergen-free base when a patient reacts to a specific excipient in the manufactured product. The molecule is the same all-trans retinoic acid the FDA reviewed in 1971. The strength, the partners, and the base are chosen for the individual on the prescription.

This is what pharmacy looked like before mass manufacturing standardized everything to three strengths in a tube. A dermatologist writes the prescription, a pharmacist prepares it for that named patient, and modern state-board oversight keeps the work honest.

Quick Facts About Topical Tretinoin

Category: Topical retinoid (all-trans retinoic acid), RAR/RXR nuclear receptor agonist

Active ingredient: Tretinoin (all-trans retinoic acid), the natural acid metabolite of vitamin A that binds retinoic acid receptors RARα, RARβ, and RARγ on keratinocytes and dermal fibroblasts

FDA-approved branded forms: Retin-A cream and gel (0.025%, 0.05%, 0.1%) for acne (Ortho Dermatologics, originally Johnson & Johnson, 1971); Renova 0.02% and 0.05% emollient cream for photoaging (1995); Retin-A Micro 0.04% and 0.1% microsphere gel; Avita 0.025% cream and gel; Atralin 0.05% gel; Altreno 0.05% polymeric-emulsion lotion (2018); Tri-Luma triple combination cream (fluocinolone 0.01% + hydroquinone 4% + tretinoin 0.05%) for melasma [4849505152]

Route: Topical, applied once daily to clean, dry skin, typically at bedtime

Evidence posture: More than 50 years of clinical use. Vehicle-controlled trials beginning with Kligman 1986 [1] and Weiss 1988 [2] established photoaging efficacy; pivotal acne trials [1,11,12,46]; multiple phase 3 trials of the modern 0.05% lotion formulation [3,5,37,39,38,40]; AAD acne guidelines designate topical retinoids as first-line therapy [3,24,46]

FDA-approval status: Multiple manufactured tretinoin products are FDA-approved. Generic tretinoin cream and gel are widely available. Compounded tretinoin preparations are not FDA-approved. [4,8,53]

Compounded under: 503A, patient-specific prescription. Typical uses include custom intermediate strengths (0.0125%, 0.075%, 0.15%), modified-Kligman melasma combinations with hydroquinone and a topical corticosteroid, allergen-free vehicles, and tretinoin-plus-niacinamide or tretinoin-plus-azelaic-acid combinations not commercially available.

Regulatory context for combinations: Hydroquinone was removed from over-the-counter sale by the September 2020 CARES Act amendments to the OTC monograph system; FDA-approved prescription hydroquinone remains Tri-Luma's combination component only. Compounded modified-Kligman creams therefore now require a Rx for the hydroquinone component as well as the tretinoin. [52]

SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY

Topical Tretinoin described in this monograph is a 503A compounded preparation. Every dose is made on a prescription, for a named patient, by a licensed pharmacist. It is not a stocked, mass-manufactured product.

- **Made to order, not off a shelf.** No batch sits in a warehouse waiting for buyers. Your prescription triggers the prep.
- **Named-patient label.** The bottle carries one patient's name. The batch records carry one prescription.
- **Dose, strength, and route chosen for the patient.** A prescriber decides what gets compounded, not a manufacturer who set the strength for a trial population.
- **Licensed pharmacist on the hook.** A real person, with a license that can be pulled, signs off on every prep. State inspectors check the facility.
- **Compounded drugs are not FDA-approved.** They should not be evaluated using branded-drug trial data alone. Availability varies by state and prescribed medication.

How This Differs from a Research-Use-Only Website

A research-use-only website ships a vial from a warehouse. There is no prescription, no pharmacist, no facility inspection, and no way to recall the product if something is wrong with it. If the vial is mislabeled, contaminated, or under-potent, there is nobody whose license is at stake.

A 503A compounding pharmacy is the other thing. The doctor writes the prescription. A licensed pharmacist, whose name is on the label, prepares the medicine in a facility the state inspects. If something goes wrong, there is a person and a license on the hook, and a documented chain of custody on every lot. That accountability is what makes it safe.

What is Topical Tretinoin?

Tretinoin is all-trans retinoic acid, the carboxylic-acid metabolite of vitamin A (retinol). Chemically it is (2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid. Unlike retinol and retinyl esters, which require two enzymatic oxidation steps in skin to become active, tretinoin acts directly on the nuclear retinoic acid receptors and produces measurable epidermal and dermal effects within weeks of topical application [4][8].

The molecule was first synthesized in the late 1940s and was developed for dermatologic use through the 1960s by Albert Kligman and James Fulton at the University of Pennsylvania. Their work supported the original 1971 FDA approval of Retin-A cream and gel for acne vulgaris by Ortho Pharmaceutical (now Ortho Dermatologics). The serendipitous observation that long-term acne patients on tretinoin showed improvement in fine wrinkles and mottled pigmentation [1] led to the photoaging research program that produced Renova (1995, first FDA-approved drug for the cutaneous signs of photoaging) [4][9][5][0][4][2].

Modern manufactured products span multiple vehicles and strengths: Retin-A cream and gel at 0.025%, 0.05%, and 0.1%; Renova 0.02% and 0.05% emollient cream; Retin-A Micro 0.04% and 0.1% microsphere gel; Avita cream and gel; Atralin 0.05% gel; and Altreno 0.05% polymeric-emulsion lotion (FDA approval 2018) [5][1]. Tri-Luma combines tretinoin 0.05% with hydroquinone 4% and fluocinolone acetonide 0.01% in a single FDA-approved cream for short-term melasma [4][8][5][2][4][4].

How Topical Tretinoin Works

Tretinoin binds the three retinoic acid receptor subtypes (RARα, RARβ, RARγ), which then heterodimerize with the retinoid X receptors (RXR) and act as ligand-activated transcription factors on retinoic-acid response elements in genomic DNA [9]. RARγ is the dominant retinoid receptor in human epidermis. Through this pathway tretinoin reprograms the transcription of genes governing keratinocyte proliferation and differentiation, follicular epithelial cohesiveness, melanocyte activity, and dermal matrix protein synthesis [3][3] [4][8].

Clinically observable effects fall into three pharmacologic domains. (1) Acne: tretinoin normalizes the abnormal follicular keratinization that produces microcomedones, dislodges existing comedones, reduces sebaceous gland inflammation, and potentiates the penetration and activity of other topical anti-acne agents [3][2][4][6] [1]. (2) Photoaging: tretinoin reverses several histologic and clinical features of UV damage, fine wrinkles, sallowness, mottled hyperpigmentation, surface roughness, and dermal atrophy, through compaction of the stratum corneum, normalization of keratinocyte atypia, induction of new collagen I/III and anchoring fibrils, suppression of UV-induced matrix metalloproteinases, and reduction of melanocyte hyperactivity [1][7][4][5][2]. (3) Pigmentation: tretinoin inhibits tyrosinase transcription, accelerates epidermal turnover, and disperses melanosomes; in combination with hydroquinone and a low-potency corticosteroid

(the classic 'Kligman formula') it remains the most effective topical regimen for melasma and post-inflammatory hyperpigmentation [7,14,16].

Biological Role of Topical Tretinoin

Vitamin A (retinol) is essential for vision, embryonic development, immune function, epithelial maintenance, and reproduction. In skin and other epithelia, dietary retinol is converted in two enzymatic steps, retinol → retinaldehyde → retinoic acid, to all-trans retinoic acid, which is the endogenous ligand of the RAR family. Endogenous tretinoin maintains normal epidermal differentiation, sebaceous gland function, and dermal collagen homeostasis at baseline; deficiency of vitamin A produces follicular hyperkeratosis (phrynoderma) and dry, scaly skin [3,3].

Topical pharmacologic dosing with tretinoin supplies a supraphysiologic concentration of the active receptor ligand directly to skin, bypassing systemic vitamin A metabolism and the conversion steps required by retinol-based cosmetic products [3,3]. This is why topical tretinoin produces measurable histologic and clinical effects within 8, 12 weeks while over-the-counter retinol products generally require six months or more for comparable changes [2,2,2,9,21].

Detailed Mechanism of Topical Tretinoin

Retinoic acid receptors are members of the steroid/thyroid hormone receptor superfamily and act as ligand-activated transcription factors [10]. In human skin RARα and RARγ are expressed in both epidermis and dermis, with RARγ accounting for an estimated 80, 90% of the nuclear retinoid receptor pool in epidermal keratinocytes. Tretinoin binds each RAR subtype with high affinity. The RAR-RXR heterodimer recruits coactivator complexes to retinoic-acid response elements in promoter regions of target genes that control terminal keratinocyte differentiation (involucrin, transglutaminase, loricrin), epidermal turnover, sebogenesis, melanogenesis (tyrosinase, TRP-1), and dermal extracellular-matrix metabolism (procollagen-1, procollagen-3, MMP-1, MMP-3, MMP-9, TIMP-1) [3,3,9,3,1].

The Fisher and Voorhees group at Michigan characterized the molecular pathology of photoaging in a series of human-skin biopsy studies [10]. UV irradiation activates EGF and other surface receptors that converge on the c-Jun N-terminal kinase (JNK) and p38 MAP kinase cascades, leading to AP-1 transcription factor activation and induction of MMP-1 (interstitial collagenase), MMP-3 (stromelysin), and MMP-9 (gelatinase B) in dermal fibroblasts and overlying keratinocytes [8,9]. The cumulative result of repeated UV exposure is degradation of mature collagen, disorganized elastin, reduced procollagen synthesis, and the histologic and clinical phenotype of photoaged skin. Pretreatment of human skin with topical tretinoin substantially blocks UV induction of MMP-1, MMP-3, and MMP-9, and restores procollagen-1 expression toward baseline; tretinoin also suppresses the negative collagen-homeostasis regulator CCN1 (cysteine-rich protein 61) in aged and photoaged skin [3,1,4,5]. Histologic studies of long-term tretinoin treatment of chronologically

aged skin [6] demonstrate compaction of the stratum corneum, new collagen deposition in the papillary dermis, and dilatation of dermal capillaries [6 16].

In acne, tretinoin normalizes the abnormal cohesiveness of follicular keratinocytes that produces the microcomedone, the precursor of all clinical acne lesions. By restoring orderly desquamation in the follicular infundibulum, tretinoin prevents new comedo formation and dislodges existing closed comedones (whiteheads), which is observed clinically as an initial 'pseudo-flare' before sustained improvement [4244]. Tretinoin also potentiates the penetration of topical antibiotics and benzoyl peroxide, which is the basis for fixed-combination products that pair tretinoin with clindamycin or benzoyl peroxide [4628]. In melasma and post-inflammatory hyperpigmentation, tretinoin acts through three additive mechanisms, accelerated epidermal turnover that physically removes melanin-laden keratinocytes, direct inhibition of tyrosinase transcription, and dispersion of melanosomes within keratinocytes, which is why the modified-Kligman combination with hydroquinone (a tyrosinase inhibitor) and a low-potency corticosteroid (which damps the inflammatory drive of melanocyte hyperactivity) outperforms each component as monotherapy [10 1714].

Topical Tretinoin Research History

Tretinoin's modern dermatologic story begins in the 1960s at the University of Pennsylvania, where Albert Kligman and James Fulton developed topical formulations of all-trans retinoic acid and demonstrated efficacy for acne vulgaris [353739]. Ortho Pharmaceutical licensed the work and obtained FDA approval for Retin-A cream and gel in 1971, the first prescription topical retinoid. Through the 1970s and early 1980s tretinoin was used almost exclusively for acne, alongside topical antibiotics, benzoyl peroxide, and a small set of keratolytics [42 2625].

The serendipitous photoaging observation came from Kligman's acne clinic: older female patients who had been on long-term tretinoin for adult acne reported improvement in fine wrinkles, brown spots, and skin texture. The Kligman et al. 1986 open-label series in the Journal of the American Academy of Dermatology [1] documented these changes in 30 adults with photoaged skin and proposed tretinoin as a treatment for the cutaneous signs of UV damage. The Weiss et al. 1988 double-blind vehicle-controlled trial in JAMA [2] established efficacy in a randomized design, and the Ellis et al [2324]. 1990 extension demonstrated that improvement was sustained for at least 22 months of continued therapy [3]. The Olsen et al. 1992 multicenter trial of a new emollient-cream vehicle (0.05% in a cosmetic-grade base) [4] provided the pivotal evidence for the Renova approval, the first drug indication for the cutaneous signs of photoaging, granted in 1995.

Parallel mechanistic work by the Voorhees and Fisher group at Michigan characterized the UV-AP-1-MMP axis of photoaging [8910] and demonstrated that topical tretinoin blocks the UV induction of MMP-1, MMP-3, and MMP-9 in human skin in vivo, providing molecular substrate for the clinical observations. Subsequent work [31] identified additional collagen-homeostasis pathways modulated by retinoids. The Kligman et al. 1975 'depigmenting formula' [15], tretinoin 0.1% + hydroquinone 5% + dexamethasone 0.1%, established the 'Kligman formula' framework for compounded melasma treatment [38]. Subsequent vehicle-controlled

tretinoin-monotherapy trials for melasma [7], modified-Kligman protocols in pigmented skin populations [14], and the pivotal Tri-Luma trials [1617] anchored the modern combination approach.

Acne formulation work accelerated through the late 1990s and 2000s. Lucky et al. 1998 published large multicenter vehicle-controlled trials of 0.025% cream [11] and 0.025% gel [12] that confirmed efficacy at the lower strength used in routine practice. Retin-A Micro (microsphere-encapsulated tretinoin, Ortho-McNeil/Galderma) was introduced to reduce vehicle irritation while preserving efficacy [4330]. Atralin (0.05% gel in an emollient base, 2007) and Altreno (0.05% polymeric-emulsion lotion, FDA approval 2018) further reduced retinoid dermatitis. The Altreno phase 3 program reported efficacy and tolerability across age, sex, and racial subgroups [404128]. The Reynolds 2024 update to the AAD acne guidelines [46] confirmed topical retinoids as first-line acne therapy on the basis of cumulative evidence since the 2016 Zaenglein guidelines [32]. The Siddiqui 2024 systematic review [47] compared tretinoin to other topical therapies for photoaging, and the Samuel 2005 Cochrane review [19] integrated the photoaging literature [36].

Topical Tretinoin Timeline

1971 • FDA approves Retin-A (tretinoin cream and gel, 0.025%/0.05%/0.1%) for acne vulgaris, the first prescription topical retinoid [4842]. Originally Ortho Pharmaceutical (later Ortho Dermatologics).

1975 • Kligman, Willis & Pathak publish the 'depigmenting formula' (tretinoin 0.1% + hydroquinone 5% + dexamethasone 0.1%) in Archives of Dermatology, the original Kligman formula for melasma and hyperpigmentation [15]

1986 • Kligman et al [1]. publish the photoaging landmark in J Am Acad Dermatol, open-label series showing tretinoin improves fine wrinkles, mottled pigmentation, and skin texture in adults with sun-damaged skin

1988 • Weiss et al [2]. publish the first double-blind vehicle-controlled trial of tretinoin for photoaged skin in JAMA, establishes randomized-trial efficacy

1990 • Ellis et al [3]. publish the extension trial in J Am Acad Dermatol showing sustained improvement at 22 months of continued tretinoin therapy for photoaged skin

1992 • Olsen et al [4]. publish the pivotal emollient-cream trial in J Am Acad Dermatol, supports the Renova approval pathway. Kligman publishes a contemporary review in Drugs & Aging [5].

1993 • Griffiths et al. publish the vehicle-controlled trial of topical tretinoin for melasma in Br J Dermatol [7]. Kligman publishes the chronoaged-skin biopsy study (non-sun-exposed elderly skin) in J Am Acad Dermatol [6].

1995 • FDA approves Renova (tretinoin 0.05% emollient cream) for the cutaneous signs of photoaging, the first FDA-approved drug for photoaging [49]

1997 • Fisher et al [8]. publish the photoaging pathophysiology framework in NEJM, UV induces AP-1, MMPs, and collagen degradation; tretinoin blocks the cascade

1998 • Lucky et al. publish two large multicenter double-blind vehicle-controlled trials of 0.025% tretinoin cream and gel for acne in J Am Acad Dermatol [1112]. Kang et al. publish the JAAD tretinoin striae trial and the modified-Kligman melasma protocol in Asian patients [1314]. Fisher et al [9]. characterize the MAP-kinase/MMP cascade in J Investig Dermatol Symp Proc.

1999 • Fisher et al [10]. publish 'Molecular mechanisms of photoaging in human skin in vivo and their prevention by all-trans retinoic acid' in Photochem Photobiol, the molecular synthesis paper

2002 • FDA approves Retin-A Micro (tretinoin microsphere gel 0.04% and 0.1%), microsphere encapsulation reduces vehicle irritation [5023]

2003 • Taylor et al. publish the pivotal Tri-Luma trial in Cutis, fluocinolone 0.01% + hydroquinone 4% + tretinoin 0.05% for moderate-to-severe melasma [1652]. FDA approval follows.

2004 • Jarratt publishes the Solagé (mequinol 2% + tretinoin 0.01%) solar lentigines trial in Cutis, alternative to hydroquinone for benign hyperpigmented macules [18]

2005 • Samuel et al. publish the Cochrane 'Interventions for photodamaged skin' systematic review [19]. Draelos et al. publish the head-to-head of hydroquinone/retinol vs tretinoin emollient cream in hyperpigmented photodamaged skin [20]. Torok et al. publish the 12-month Tri-Luma extension [17].

2006 • Mukherjee et al [21]. publish 'Retinoids in the treatment of skin aging' in Clinical Interventions in Aging, the clinical-efficacy and safety synthesis

2007 • FDA approves Atralin (tretinoin 0.05% gel in an emollient base) for acne [5024]. Kafi et al. publish the topical retinol trial in Arch Dermatol [22]. Berger et al. publish the tretinoin microsphere 0.04% pivotal trial and the head-to-head with 0.1% microsphere [23].

2008 • Nighland et al. publish the meta-analysis of tretinoin microsphere gel for facial acne [25]. Jorizzo et al. report tretinoin microsphere in younger acne patients [26]. Rendon et al. publish the triple-combination plus glycolic-acid-peels pilot for moderate-to-severe melasma [27].

2009 • Leyden et al [28]. compare clindamycin/tretinoin gel vs tretinoin microsphere vs adapalene in J Drugs Dermatol

2010 • Babamiri et al. publish the cosmeceuticals retinoids evidence review [29]. Leyden et al. compare tretinoin microsphere pump vs adapalene + benzoyl peroxide gel [30].

2011 • Quan et al [31]. (Exp Dermatol) demonstrate that retinoids suppress CCN1 (cysteine-rich protein 61), a negative regulator of collagen homeostasis, in aged human skin

2016 • American Academy of Dermatology publishes Guidelines of Care for the Management of Acne Vulgaris (Zaenglein et al., JAAD), topical retinoids designated first-line therapy [32]. Riahi et al. publish the topical retinoids mechanism review [33].

2018 • FDA approves Altreno (tretinoin 0.05% polymeric-emulsion lotion), first lotion-vehicle tretinoin, designed for once-daily acne treatment with reduced retinoid dermatitis [51]. Bagatin et al. publish the adapalene 0.3% vs tretinoin 0.05% photoaging head-to-head [34].

2019 • Phase 3 Altreno subgroup analyses publish in J Drugs Dermatol and J Dermatolog Treat: Cook-Bolden (Hispanic population), Han (Asian population), Harper (adult females), Lain (gender and race), Stein Gold (age), Kircik (polymeric-emulsion technology) [35][37][39][40][36].

2020 • CARES Act removes hydroquinone from over-the-counter sale, making Rx-only prescription hydroquinone (including the Tri-Luma combination and compounded modified-Kligman creams) the only legal pathway. Harper et al. publish the tretinoin lotion subgroup tolerability paper [41].

2021 • Baldwin publishes '50 Years of Topical Retinoids for Acne: Evolution of Treatment' in Am J Clin Dermatol, anniversary review of tretinoin since the 1971 Retin-A approval [42]

2022 • Draelos publishes the tretinoin lotion vs generic cream tolerability and patient-preference comparison in J Drugs Dermatol [43]

2023 • Baldwin publishes the contemporary tretinoin formulations review in J Drugs Dermatol [44]. Sadick publishes the topical-treatments review for melasma and post-inflammatory hyperpigmentation [45].

2024 • AAD updates the acne vulgaris guidelines (Reynolds et al., JAAD), topical retinoids remain first-line [46]. Siddiqui et al. publish the systematic review comparing tretinoin to other topical photoaging therapies in Am J Clin Dermatol [47].

Clinical Contexts for Topical Tretinoin

Acne vulgaris FDA APPROVED

FDA-approved indication for multiple manufactured tretinoin products; first-line therapy per AAD guidelines.

Tretinoin is FDA-approved for acne vulgaris under multiple manufactured products: Retin-A (1971, 0.025%/0.05%/0.1% cream and gel), Retin-A Micro (microsphere gel 0.04% and 0.1%), Avita, Atralin (0.05% gel), and Altreno (0.05% polymeric-emulsion lotion, 2018) [23][24][25]. The 1998 Lucky et al [51]. double-blind vehicle-controlled trials [11][12] established efficacy at 0.025% in both cream and gel vehicles [48]. The 2018-onward Altreno phase 3 program demonstrated efficacy and improved tolerability across Hispanic [35], Asian [37], female [39], gender/race [38], and age [40] subgroups; vehicle technology is reviewed in Kircik 2019 [36] and Draelos 2022 [43]. The microsphere program established reduced irritation at preserved efficacy [28][30][50]. The 2024 AAD acne guidelines [46] (updating 2016 [32]) designate topical retinoids as first-line for inflammatory and comedonal acne, alone or in fixed combination with benzoyl peroxide or clindamycin [26].

Branded product: Retin-A, Retin-A Micro, Avita, Atralin, Altreno (multiple manufacturers; generics widely available)

Cutaneous signs of photoaging (fine wrinkles, mottled hyperpigmentation, surface roughness) FDA APPROVED

FDA-approved indication for Renova (tretinoin 0.05% emollient cream) as adjunct to a comprehensive skincare and sun-avoidance program.

Renova was the first drug approved for the cutaneous signs of photoaging (FDA 1995, tretinoin 0.05% emollient cream) [10][49]. The Kligman 1986 open-label series [1], the Weiss 1988 double-blind vehicle-controlled trial in JAMA [2], the Ellis 1990 long-term extension [3], and the Olsen 1992 emollient-cream pivotal trial [4] together established the photoaging evidence base. The Kligman 1993 chronoaged-skin biopsy study [6] demonstrated dermal new collagen deposition in non-sun-exposed elderly skin [8][9]. Mechanistic work characterized UV-AP-1-MMP induction and tretinoin's suppression of MMP-1, MMP-3, and MMP-9 [31]. The Samuel 2005 Cochrane systematic review [19] and the Siddiqui 2024 comparative systematic review [47] integrated subsequent literature, and the Bagatin 2018 head-to-head [34] compared adapalene 0.3% with tretinoin 0.05% in photoaging.

Branded product: Renova (tretinoin 0.05% emollient cream, Ortho Dermatologics)

Moderate-to-severe facial melasma (short-term) FDA APPROVED

FDA-approved indication for Tri-Luma triple combination cream (fluocinolone 0.01% + hydroquinone 4% + tretinoin 0.05%).

Tri-Luma was approved in 2002 on the basis of the Taylor 2003 pivotal trial [16] for short-term treatment of moderate-to-severe melasma of the face. The 12-month Torok extension [17] supported maintenance dosing. Tretinoin monotherapy for melasma is supported by the Griffiths 1993 vehicle-controlled trial [7 52]. The Kang 1998 modified-Kligman protocol [14] demonstrated efficacy in pigmented Asian skin. The Rendon 2008 combination-with-peels pilot [27] and the Sadick 2023 topical-treatments review [45] situate the triple-combination approach in current melasma practice.

Branded product: Tri-Luma (fluocinolone acetonide 0.01% / hydroquinone 4% / tretinoin 0.05%, Galderma)

Solar lentigines and benign hyperpigmented macules WELL STUDIED

FDA-approved combination Solagé (mequinol 2% + tretinoin 0.01% solution) was approved historically; trial evidence supports tretinoin-containing combinations for solar lentigines.

Jarratt 2004 [18] reported that mequinol 2% / tretinoin 0.01% solution (Solagé) was effective and safe for solar lentigines, with an irritation profile favorable to hydroquinone 3%. The product is no longer marketed in the United States, leaving compounded mequinol/tretinoin and hydroquinone/tretinoin combinations as the patient-specific options for this indication.

Striae distensae (stretch marks), early erythematous striae WELL STUDIED

Off-label; supported by a placebo-controlled trial in early erythematous striae.

Kang et al. 1998 [13] reported that topical tretinoin 0.1% applied to early erythematous striae for 24 weeks produced clinically and histologically significant improvement in length and width compared with vehicle. Established mature white striae respond poorly. Combination with energy-based devices is the current adjunct in resistant cases.

Post-inflammatory hyperpigmentation WELL STUDIED

Off-label; supported by clinical trials of tretinoin monotherapy and combination protocols.

Post-inflammatory hyperpigmentation responds to tretinoin monotherapy and to modified-Kligman triple-combination protocols by the same mechanisms as melasma, accelerated epidermal turnover, tyrosinase inhibition, and melanosome dispersion [4 5 14 20].

Off-Label Uses of Topical Tretinoin

Mottled hyperpigmentation in skin of color (modified-Kligman compounded protocols)

WELL STUDIED

Off-label; widely used and supported by trial evidence for combination tretinoin-plus-hydroquinone-plus-corticosteroid creams.

Modified-Kligman compounded creams pairing tretinoin (typically 0.025, 0.1%) with hydroquinone (typically 4, 6%) and a low-potency corticosteroid (e.g., hydrocortisone 1% or fluocinolone 0.01%) remain the gold-standard topical approach for moderate-to-severe melasma and post-inflammatory hyperpigmentation in pigmented skin populations [14][16][17][27][45][15].

Early striae distensae

WELL STUDIED

Off-label; supported by a placebo-controlled trial.

Kang 1998 [13] demonstrated benefit for early erythematous striae at 0.1% over 24 weeks. Mature white striae respond poorly.

Field-cancerization adjunct / actinic keratosis context

EMERGING

Off-label; trial evidence is limited and not a substitute for field therapies with FDA-approved indications.

A randomized evaluator-blinded trial compared 0.05% tretinoin cream with a 5% tretinoin peel for photoaging and field cancerization of the forearms with histologic endpoints. Tretinoin is sometimes used as an adjunct to FDA-approved field therapies (5-fluorouracil, imiquimod, photodynamic therapy), but as a standalone field-treatment indication it remains investigational [47].

FDA-Approved Uses of Topical Tretinoin

Brand	Indication	Year	Route
Retin-A	Acne vulgaris	1971	topical
Renova	Photoaging (fine wrinkles, mottled hyperpigmentation, tactile roughness)	1995	topical
Retin-A Micro	Acne vulgaris	1997	topical
Atralin	Acne vulgaris	2007	topical
Altreno	Acne vulgaris (lotion)	2018	topical
Vesanoid	Acute promyelocytic leukemia (APL)	1995	oral

Compounded Topical Tretinoin (503A)

Compounded topical tretinoin is dispensed under 503A on a patient-specific prescription when the prescribing clinician documents that no FDA-approved manufactured product is clinically appropriate [1239]. The most common documented reasons are (1) a strength not commercially available, e.g., 0.0125% for retinoid-naïve patients with sensitive skin who do not tolerate 0.025%, or 0.075, 0.15% for established users who have plateaued at 0.1%; (2) a vehicle without a specific allergen, e.g., fragrance-free, parabens-free, or propylene-glycol-free bases for patients with documented contact sensitization; (3) a multi-ingredient preparation that does not exactly match an FDA-approved single product, most importantly the classic Kligman formula (tretinoin + hydroquinone + a topical corticosteroid) for melasma and post-inflammatory hyperpigmentation, and tretinoin-plus-niacinamide or tretinoin-plus-azelaic-acid combinations [151445].

The regulatory context for the hydroquinone-containing combinations changed materially in 2020. Before the September 2020 CARES Act amendments to the OTC monograph system, hydroquinone 2% creams were sold over-the-counter and 4% products were available by prescription. The CARES Act removed hydroquinone from OTC sale entirely, leaving prescription hydroquinone in Tri-Luma and compounded modified-Kligman creams as the only legal pathways [11]. This makes the 503A compounded modified-Kligman cream a more central clinical option than it was a decade ago, because patients can no longer self-treat with over-the-counter hydroquinone and the FDA-approved single product (Tri-Luma) is indicated only for short-term use at fixed concentrations [4].

Compounded tretinoin preparations are not bioequivalent to Retin-A, Retin-A Micro, Renova, Avita, Atralin, Altreno, or Tri-Luma. Vehicle, concentration, container closure, and excipients differ. The published efficacy and safety evidence for the manufactured products does not transfer to a compounded preparation without local stability data and the prescriber's clinical judgment [161712]. RonanRx documents the patient-specific rationale, sources active pharmaceutical ingredient (API) from FDA-registered facilities with certificates of analysis, prepares under USP <795> for nonsterile topical compounding, and assigns beyond-use dates with documented stability support per state board of pharmacy expectations [555354].

Topical Tretinoin Formulations and Routes

Form	Concentration	Description
Compounded topical cream	Custom, typical strengths 0.0125%, 0.025%, 0.05%, 0.075%, 0.1%, 0.15%	Nonsterile topical cream prepared under USP <795> with documented API source, batch records, and beyond-use dating. Used when a manufactured strength is not commercially available, when a vehicle without a specific allergen is required, or as a base for multi-ingredient

Form	Concentration	Description
		preparations (modified-Kligman with hydroquinone + corticosteroid; tretinoin + niacinamide; tretinoin + azelaic acid). [55]
Compounded topical gel	Custom, typical strengths 0.025%, 0.05%, 0.1%	Alcohol- or hydroalcoholic-base gel for acne-prone or oily-skin patients. Compounded equivalent of Retin-A gel but with custom strength or alternative excipients. [55]
Manufactured cream (reference product)	0.025%, 0.05%, 0.1% (Retin-A); 0.02%, 0.05% (Renova emollient cream); 0.025% (Avita)	FDA-approved manufactured Retin-A, Renova, and Avita creams. Retin-A is labeled for acne; Renova for the cutaneous signs of photoaging; Avita for acne. Generic equivalents are widely available. [4849]
Manufactured gel (reference product)	0.025%, 0.05%, 0.1% (Retin-A); 0.025% (Avita); 0.05% (Atralin emollient gel)	FDA-approved manufactured gel formulations for acne. Atralin is a 0.05% emollient gel with reduced retinoid dermatitis. [4850]
Manufactured microsphere gel (reference product)	0.04%, 0.1% (Retin-A Micro)	Tretinoin encapsulated in porous methylmethacrylate-glycol-dimethacrylate copolymer microspheres for controlled release into the stratum corneum and reduced vehicle irritation. Multiple comparative trials [23242625283 0] support reduced irritation vs older vehicles at preserved efficacy.
Manufactured polymeric-emulsion lotion (reference product)	0.05% (Altreno, Ortho Dermatologics; FDA approval 2018)	Tretinoin in a polymeric-emulsion lotion vehicle that disperses small droplets of active in a moisturizing aqueous base. The vehicle was designed to reduce retinoid dermatitis and improve adherence for daily acne therapy [36393537384041 43]. [51]
Manufactured triple-combination cream (reference product)	Fluocinolone acetonide 0.01% + hydroquinone 4% + tretinoin 0.05% (Tri-Luma, Galderma)	FDA-approved cream for short-term treatment of moderate-to-severe melasma of the face. Pivotal Taylor 2003 trial [16] supports 8-week efficacy; the Torok 2005 extension [17] supports up to 12 months of intermittent maintenance. [52]
Compounded modified-Kligman cream	Tretinoin 0.025, 0.1% + hydroquinone 4, 6% + a low- to mid-potency corticosteroid (e.g., hydrocortisone 1%, fluocinolone 0.01%, or triamcinolone 0.025%)	Patient-specific compounded variation on the classic Kligman 1975 formula [15] and the FDA-approved Tri-Luma combination [52]. Used when individual component strengths or the corticosteroid choice need to be tailored to the patient's skin phototype, melasma severity, and tolerance. Prepared under USP <795>. [16171455]

Routes used in published literature: topical.

Topical Tretinoin Dosing

Route	Population	Range	Duration	Study type
Topical	Adults with acne vulgaris	Apply a pea-sized amount of 0.025, 0.1% cream or gel (or 0.04, 0.1% microsphere gel, or 0.05% Altreno lotion) to the entire affected area once daily at bedtime. Start at the lowest strength and increase as tolerated; if irritation develops, decrease frequency to every other or every third night before discontinuing.	12 weeks to clinically significant improvement; continued indefinitely as maintenance per AAD guidelines	FDA-approved labeled regimen and AAD acne guidelines
Topical	Adults with cutaneous signs of photoaging	Apply a pea-sized amount of Renova 0.02% or 0.05% emollient cream (or compounded equivalent) to clean dry facial skin once daily at bedtime, as adjunct to a comprehensive skincare and sun-avoidance program including broad-spectrum SPF 30+ daily	Continuous use; trials demonstrate continued improvement out to 22 months [3]; clinical practice continues indefinitely	FDA-approved labeled regimen (Renova) and supporting trials
Topical	Adults with moderate-to-severe facial melasma	Tri-Luma cream (fluocinolone 0.01% + hydroquinone 4% + tretinoin 0.05%), apply a thin film to affected areas once daily at bedtime for up to 8 weeks. The 12-month extension [17] supports intermittent maintenance dosing under prescriber supervision.	8 weeks initial; intermittent maintenance per prescriber	FDA-approved labeled regimen
Topical	Adults with early erythematous striae distensae	Tretinoin 0.1% cream applied once daily for 24 weeks (Kang 1998 trial regimen)	24 weeks	Single placebo-controlled randomized trial

Tretinoin is doctor-prescribed and titrated by tolerability. The standard initiation pattern is once-daily application of a pea-sized amount of the lowest available strength (often 0.025% for acne or 0.02% Renova for photoaging) to clean, dry skin 20, 30 minutes before bedtime, on top of a bland moisturizer if needed. Most patients experience an initial 'retinoid dermatitis' window of 2, 6 weeks (erythema, scaling, dryness, transient acne flare), which improves with continued use; titration up to 0.05% and 0.1% strengths is appropriate once the lower strength is tolerated [46]. Daily broad-spectrum sunscreen (SPF 30 or higher) is required during therapy because tretinoin increases UV sensitivity [48495].

Compounded tretinoin preparations should mirror the manufactured-product titration pattern unless the prescriber documents a patient-specific reason for variance (e.g., an intermediate strength of 0.0125% or 0.075% for tolerance titration, or a higher strength of 0.15% for plateau patients on 0.1%) [5][24][4]. Modified-Kligman compounded creams for melasma are typically prescribed for an initial 8, 12 week intensive phase followed by intermittent maintenance, with periodic re-evaluation of pigmentary response and corticosteroid burden.

Topical Tretinoin Safety

The dominant safety concern with topical tretinoin is retinoid dermatitis, erythema, scaling, dryness, burning, stinging, and transient acne flare during the first 2, 6 weeks of therapy [5][2] [2][3][24]. Across the manufactured-product trials, local irritation events are reported in 25, 60% of users in the first month and decrease substantially with continued use. The polymeric-emulsion lotion (Altreno) and emollient bases (Atralin, Renova) were specifically developed to reduce this dermatitis [3][6][4][3][4]. Microsphere encapsulation (Retin-A Micro) similarly attenuates vehicle irritation at preserved efficacy [2][5][2][8][3][0].

Tretinoin increases UV sensitivity. All patients should use daily broad-spectrum sunscreen of SPF 30 or higher, avoid deliberate tanning, and minimize sun exposure during peak hours. Application is timed to evening because tretinoin is also photolabile and decomposes on direct UV exposure on the skin surface [3][3][4][4][5][2]. Skin bleaching of treated areas, hypopigmentation, and post-inflammatory hyperpigmentation in skin of color are uncommon but reported, particularly when used without titration in pigmented skin types.

Systemic absorption from topical application is minimal but not zero. The Mounjaro/Zepbound-style pregnancy categorization does not apply here; topical tretinoin is FDA pregnancy category C (manufactured products) and the prescribing information advises against use during pregnancy because oral isotretinoin (a related but distinct retinoid) is a known human teratogen [5][2] [3][9][3][5]. Although epidemiologic data have not established a malformation signal with topical tretinoin specifically, the conservative position adopted by all FDA-approved labels is to discontinue during pregnancy and breastfeeding [4][8][4][9][5][1].

Compounded tretinoin preparations carry the additional consideration that vehicle, concentration, container closure, and excipients may differ from any FDA-approved reference product [3][7][3][8]. Local stability and tolerability cannot be assumed from the manufactured-product literature [4][0][4][1]. Modified-Kligman compounded creams add the safety profile of hydroquinone (ochronosis with prolonged high-strength use; skin irritation; rare contact sensitization) and a low-potency corticosteroid (skin atrophy with prolonged use), which is why these compounded preparations are typically prescribed for an initial intensive phase with planned re-evaluation [5][2] [1][1][1][2].

Contraindications

Topical tretinoin is contraindicated in patients with known hypersensitivity to tretinoin or any excipient in the manufactured product or compounded preparation [4][8][4][9][5][1]. The labels of all manufactured products

advise against use during pregnancy and breastfeeding, and against use on broken, eczematous, severely sunburned, or actively inflamed skin.

Compounded modified-Kligman creams that include hydroquinone are contraindicated in patients with known hydroquinone hypersensitivity, exogenous ochronosis (a paradoxical bluish-black hyperpigmentation associated with prolonged high-strength hydroquinone use, more common in skin of color), and in pregnancy and breastfeeding [52].

Drug interactions

Topical tretinoin has minimal systemic absorption and does not have clinically significant systemic drug-drug interactions through cytochrome P450 metabolism [48]. The relevant interactions are topical co-application interactions and photosensitization additive effects.

Concurrent topical benzoyl peroxide oxidizes tretinoin in some vehicles, reducing potency; for this reason fixed-combination products co-formulate the two in stabilized vehicles, and patients using both as separate products should apply them at different times of day (typically benzoyl peroxide in the morning, tretinoin at bedtime) [48]. Concurrent use with other topical irritants, alpha-hydroxy acids, beta-hydroxy acids (salicylic acid), high-concentration vitamin C serums, physical exfoliants, and abrasive cleansers, increases retinoid dermatitis and should be staggered or paused during the initiation phase. Concurrent oral isotretinoin is not a contraindication but is redundant; the two are generally not co-prescribed.

Systemic photosensitizing medications (e.g., doxycycline, thiazide diuretics, sulfonamides) increase the additive UV sensitivity of tretinoin and warrant additional sun-protection counseling [44 48 51 46].

Adverse events

The most common adverse events across the manufactured-product trials are local: erythema, peeling/scaling, dryness, burning, stinging, and itching at the application site. In the Lucky 1998 cream and gel pivotal trials for acne [11 12], local irritation occurred in 30, 50% of tretinoin-treated participants vs 10, 15% on vehicle, and decreased with continued use [35]. In the Altreno phase 3 program, local tolerability scores improved between week 4 and week 12, and treatment-related discontinuation rates were 1, 4% across subgroups [39 40 41].

Tretinoin increases UV sensitivity; sunburn events are more common when sun-protection counseling is inadequate [38]. Transient acne flare in the first 2, 6 weeks is a recognized adaptation pattern, not an indication to discontinue, and reflects mobilization of pre-existing closed comedones [42 44 37]. Skin lightening of treated areas and post-inflammatory hyperpigmentation in pigmented skin types are uncommon but reported, particularly when used at high strength without adequate titration.

For modified-Kligman compounded combinations, the adverse-event profile adds the components of hydroquinone (occasional contact dermatitis; rare exogenous ochronosis with prolonged high-strength use) and topical corticosteroid (skin atrophy, telangiectasias, perioral dermatitis with prolonged use, particularly

on facial skin), which is why these compounded preparations are typically prescribed for time-limited intensive phases [16][17][45].

Monitoring Topical Tretinoin Therapy

Baseline assessment should include the patient's skin phototype, prior retinoid exposure and tolerance, baseline pigmentary lesions if treating melasma or post-inflammatory hyperpigmentation, current photosensitizing medications, and pregnancy status in patients of reproductive potential [4][8].

On therapy, in-person or telehealth re-evaluation at 4, 8, and 12 weeks is appropriate to assess tolerability, titrate strength or frequency, and document response. For modified-Kligman compounded creams used for melasma, a planned re-evaluation at 8, 12 weeks is essential to limit cumulative corticosteroid exposure and to plan the maintenance phase [46][44]. Patients should be counseled to expect the initial retinoid-dermatitis window, to use broad-spectrum SPF 30+ daily, and to report unexpected hyperpigmentation, persistent burning, or hypopigmentation [48][51][52].

Topical Tretinoin in Special Populations

Topical Tretinoin Evidence Quality

Tretinoin has one of the largest and longest-running evidence bases in dermatology [5][4] [35][37][8]. The acne indication is supported by the original 1971 Retin-A approval, the Lucky 1998 double-blind vehicle-controlled cream and gel trials [11][12], multiple subsequent vehicle iterations (microsphere, emollient gel, polymeric-emulsion lotion) with their own pivotal programs, the Nighland 2008 meta-analysis of tretinoin microsphere gel [25], and the AAD acne guidelines [32][46] which place topical retinoids as first-line therapy.

The photoaging indication is supported by the Kligman 1986 open-label series [1], the Weiss 1988 double-blind vehicle-controlled trial in JAMA [2], the Ellis 1990 sustained-improvement extension [3], the Olsen 1992 emollient-cream pivotal trial that supported the 1995 Renova approval [4], the Kligman 1993 chronoaged-skin biopsy study [6], the Samuel 2005 Cochrane systematic review [19], the Siddiqui 2024 comparative systematic review [47], and a coherent body of mechanistic work from the Voorhees and Fisher group that demonstrates UV-induced AP-1 and MMP induction in human skin and tretinoin's suppression of that cascade [54]. The melasma indication is supported by the Griffiths 1993 vehicle-controlled monotherapy trial [7], the modified-Kligman protocols [14], and the pivotal Tri-Luma trials [16][17] that produced the only FDA-approved triple-combination melasma cream.

Evidence specific to compounded preparations is, as for most compounded drugs, absent [41][36][39]. There is no parallel efficacy program for compounded tretinoin creams or modified-Kligman combinations [23][24][39][10]. Compounded use is an extrapolation from the manufactured-product evidence base, justified case by case

by patient-specific factors that the manufactured products cannot accommodate, a custom strength, an allergen-free vehicle, or a multi-ingredient combination that does not exactly match Tri-Luma or any other FDA-approved single product [54] [38] [40] [31].

Major Topical Tretinoin Clinical Studies

Study	Design	Participants	Duration	Finding
Kligman et al. (1986, J Am Acad Dermatol), Topical tretinoin for photoaged skin	Open-label clinical and histologic series in adults with photoaged facial skin	30	16 weeks	Clinical and histologic improvement in fine wrinkles, mottled hyperpigmentation, and skin texture with 0.05% tretinoin cream, the foundational photoaging observation that defined the indication [1]
Weiss et al. (1988, JAMA), Topical tretinoin double-blind vehicle-controlled photoaging trial	Double-blind, vehicle-controlled, randomized split-face trial	40	16 weeks	Significant improvement in fine wrinkles, mottled hyperpigmentation, roughness, and laxity with 0.1% tretinoin cream vs vehicle, first randomized confirmation of the photoaging effect [2]
Ellis et al. (1990, J Am Acad Dermatol), Sustained improvement with prolonged tretinoin	Open-label extension of the Weiss double-blind trial	—	22 months	Sustained improvement in photoaging endpoints with continued tretinoin therapy beyond the original double-blind period, established the chronic-use case for photoaging indication [3]
Olsen et al. (1992, J Am Acad Dermatol), Tretinoin emollient cream pivotal trial	Multicenter randomized vehicle-controlled trial of 0.05% tretinoin emollient cream	—	24 weeks	Significant improvement in photoaging clinical scores at 24 weeks with the new emollient-cream vehicle, pivotal evidence supporting the 1995 Renova FDA approval [4]
Kligman et al. (1993, J Am Acad Dermatol), Tretinoin on non-sun-exposed elderly skin	Histologic study of topical tretinoin applied to non-sun-exposed buttock skin in older adults	—	Up to 9 months	New collagen deposition in the papillary dermis of chronologically aged, non-sun-exposed skin, distinguishes

Study	Design	Participants	Duration	Finding
				intrinsic-aging effects of tretinoin from photoaging effects [6]
Griffiths et al. (1993, Br J Dermatol), Topical tretinoin for melasma	Double-blind, vehicle-controlled randomized trial of 0.1% tretinoin cream for facial melasma	—	40 weeks	Significant lightening of melasma vs vehicle with tretinoin monotherapy, established tretinoin's role in melasma treatment [7]
Lucky et al. (1998, J Am Acad Dermatol), 0.025% tretinoin cream pivotal acne trial	Multicenter double-blind vehicle-controlled parallel-group trial of 0.025% tretinoin cream in acne vulgaris	—	12 weeks	Significant reduction in inflammatory and non-inflammatory acne lesion counts with 0.025% cream vs vehicle, established the lower-strength cream as effective and widely used [11]
Lucky et al. (1998, J Am Acad Dermatol), 0.025% tretinoin gel pivotal acne trial	Multicenter double-blind vehicle-controlled parallel-group trial of two 0.025% tretinoin gels	—	12 weeks	Significant reduction in acne lesion counts vs vehicle in both gel formulations, established the lower-strength gel as a tolerable acne option [12]
Kang et al. (1998, J Am Acad Dermatol), Topical tretinoin for striae distensae	Placebo-controlled randomized trial of 0.1% tretinoin in early erythematous striae	—	24 weeks	Significant clinical and histologic improvement in early erythematous striae vs vehicle, established benefit for early-phase striae [13]
Kang et al. (1998, J Dermatol), Modified-Kligman intermittent therapy for melasma in Asian patients	Clinical and histologic study of combined topical retinoic acid + hydroquinone + hydrocortisone in Asian melasma	—	Variable	Intermittent triple-combination therapy produced melanin reduction and clinical improvement in melasma in pigmented Asian skin, extended the Kligman formula to skin of color [14]
Taylor et al. (2003, Cutis), Pivotal Tri-Luma trial for moderate-to-severe melasma	Randomized vehicle-controlled and dyad-controlled trial of fluocinolone 0.01% + hydroquinone 4% + tretinoin 0.05% cream	—	8 weeks	Significantly higher complete clearance and overall improvement rates with the triple combination than with any of its two-component dyads, pivotal evidence for the 2002 Tri-Luma FDA approval [16]

Study	Design	Participants	Duration	Finding
Torok et al. (2005, J Drugs Dermatol), Tri-Luma 12-month extension	Open-label 12-month extension of an 8-week vehicle-controlled trial	—	12 months	Maintenance of melasma clearance with intermittent triple-combination dosing over 12 months, supports extended use under prescriber supervision [17]
Samuel et al. (2005, Cochrane Database Syst Rev), Interventions for photodamaged skin	Cochrane systematic review	—	—	Topical tretinoin had the most robust evidence base for improvement in photodamaged skin among the topical interventions reviewed [19]
Berger et al. (2007, Cutis), Tretinoin microsphere 0.04% pivotal trial in adults	Double-blind randomized vehicle-controlled parallel-group multicenter trial	—	12 weeks	Significant reduction in inflammatory and non-inflammatory acne lesion counts with 0.04% microsphere gel vs vehicle, established the lower-irritation microsphere formulation in adults [23]
Nighland et al. (2008, J Drugs Dermatol), Tretinoin microsphere gel meta-analysis	Meta-analysis of randomized trials of tretinoin microsphere gel for facial acne	—	—	Confirmed efficacy across pooled trial population with consistent reduction in inflammatory and non-inflammatory lesion counts [25]
Quan et al. (2011, Exp Dermatol), Retinoids and CCN1 collagen homeostasis	Skin-equivalent culture and aged human skin in vivo, mechanistic study	—	—	Retinoids suppress CCN1, a negative regulator of collagen homeostasis, providing an additional molecular pathway for tretinoin's pro-collagen effect in aged skin [31]
Harper et al. (2019, J Drugs Dermatol), Tretinoin 0.05% lotion in adult females	Two phase 3 randomized vehicle-controlled trials, pooled subgroup analysis in adult females	—	12 weeks	Significant reduction in inflammatory and non-inflammatory acne lesion counts with 0.05% polymeric-emulsion lotion vs vehicle in adult women, with favorable tolerability, established Altreno in adult female acne population [39]
Cook-Bolden et al. (2019, J Drugs		—	12 weeks	Significant lesion reduction with Altreno vs vehicle and favorable

Study	Design	Participants	Duration	Finding
Dermatol), Tretinoin 0.05% lotion in Hispanic patients	Phase 3 vehicle-controlled subgroup analysis			tolerability in Hispanic acne patients, supports use across pigmented skin populations [35]
Stein Gold et al. (2019, J Drugs Dermatol), Tretinoin 0.05% lotion: age subgroup analysis	Phase 3 vehicle-controlled subgroup analysis stratified by age (under and over 30)	—	12 weeks	Significant lesion reduction across both age groups vs vehicle with consistent tolerability, supports use across adolescent and adult acne populations [40]
Bagatin et al. (2018, Eur J Dermatol), Adapalene 0.3% vs tretinoin 0.05% for photoaging	Randomized comparative trial of adapalene 0.3% gel vs tretinoin 0.05% cream for cutaneous photoaging	—	24 weeks	Comparable efficacy between the two topical retinoids on photoaging endpoints, supports adapalene as a tolerability-favorable alternative to tretinoin [34]
Siddiqui et al. (2024, Am J Clin Dermatol), Tretinoin vs other topical photoaging therapies systematic review	Systematic review comparing tretinoin to other topical therapies for skin photoaging	—	—	Tretinoin remained the topical agent with the most robust evidence for photoaging improvement; newer retinoids and non-retinoid topicals showed mixed comparability [47]

Topical Tretinoin Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Systemic absorption of topical tretinoin is low. Pharmacokinetic studies of manufactured creams, gels, and the polymeric-emulsion lotion document plasma tretinoin concentrations that remain within or near the endogenous range after once-daily topical application, with no clinically meaningful systemic accumulation [48][51]. Endogenous tretinoin is normally present in human plasma at low nanomolar concentrations as a vitamin A metabolite.

Within the skin, tretinoin penetrates the stratum corneum, accumulates in the epidermis and follicular epithelium, and binds nuclear retinoic acid receptors. Microsphere encapsulation (Retin-A Micro) provides controlled release into the stratum corneum, prolonging the local concentration window while reducing acute surface concentration; the polymeric-emulsion lotion vehicle (Altreno) similarly disperses small droplets of active in a moisturizing base [36][44].

Compounded preparations may differ from any FDA-approved reference product in vehicle, penetration enhancers, and concentration. Local tissue pharmacokinetics cannot be assumed to match the

manufactured-product literature without separate dermatopharmacokinetic or vasoconstrictor-style assessment.

Pharmacodynamics

Pharmacodynamic effects include normalization of follicular keratinization (basis for acne efficacy), compaction of the stratum corneum and induction of new dermal collagen (basis for photoaging efficacy), and inhibition of tyrosinase transcription with accelerated epidermal turnover (basis for hyperpigmentation efficacy) [33][89] [11].

Clinically measured endpoints in trials include investigator and patient global assessments, inflammatory and non-inflammatory acne lesion counts, melasma area-and-severity index (MASI), fine wrinkle scores, mottled hyperpigmentation scores, and histologic measurements of stratum corneum compaction and dermal procollagen-1 staining [11][216].

↓↑ Comparing Topical Tretinoin Formulations

FDA-approved manufactured tretinoin products fall into vehicle families that differ chiefly in tolerability and patient preference rather than in core efficacy [39][38][40]. Retin-A cream and gel are the original 1971 formulations and remain in use as generics [43][44]. Renova (1995) introduced an emollient-cream base specifically for the photoaging indication [30]. Retin-A Micro (microsphere gel, 0.04% and 0.1%) encapsulates tretinoin in porous copolymer microspheres for controlled release and reduced irritation [48] [36][41]. Atralin (0.05% emollient gel) and Altreno (0.05% polymeric-emulsion lotion) were further low-irritation vehicle iterations [51] [35][37].

Tri-Luma combines tretinoin 0.05% with hydroquinone 4% and fluocinolone acetonide 0.01% as the only FDA-approved triple combination for melasma [52][16][17] [49][50]. Compounded modified-Kligman creams allow the prescriber to tailor each component strength and substitute corticosteroid choice to the individual patient, most often used when Tri-Luma's fixed concentrations are not appropriate (e.g., when a lower-potency corticosteroid is needed for thin facial skin in a pigmented skin type) [14][45] [25]. Compounded preparations are not bioequivalent to any of these reference products [23][24][28].

🌡 Topical Tretinoin Storage and Handling

Manufactured tretinoin creams, gels, and lotions are stored at controlled room temperature (20, 25°C / 68, 77°F), protected from light and excessive heat. Tretinoin is photolabile and oxidatively sensitive; tubes and pumps should be kept closed and away from direct sunlight. Compounded tretinoin preparations are stored per the pharmacy's stability data and beyond-use date assignment under USP <795>, typically in light-resistant tubes or jars at room temperature [48][51][55].

Topical Tretinoin Compounding & Operations

503A compounding

Compounded topical tretinoin is prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies [54]. The dispensing pharmacy prepares nonsterile topical preparations per USP General Chapter <795>, the official compendial standard for nonsterile pharmaceutical compounding, with documented API sourcing from FDA-registered facilities, gravimetric verification, beyond-use date assignment supported by published stability or in-house stability data, and full lot traceability from API through dispensing [5553].

Modified-Kligman compounded creams that include hydroquinone and a topical corticosteroid are governed by the same USP <795> framework, with additional ingredient-identity verification for each component. The 2020 CARES Act removed hydroquinone from over-the-counter sale, which means the hydroquinone component now requires a prescription, making the documented patient-specific 503A pathway the primary route to these creams outside the FDA-approved Tri-Luma single product. Compounded preparations are not bioequivalent to any FDA-approved reference product; the prescriber and pharmacist together document the patient-specific rationale [54].

Pharmacist review

Each prescription for compounded topical tretinoin undergoes pharmacist review prior to dispensing [52]. The review confirms: a documented patient-specific clinical reason that no FDA-approved manufactured product is appropriate (custom strength, allergen-free vehicle, or multi-ingredient preparation not commercially available); absence of contraindications (hypersensitivity, pregnancy/breastfeeding for the topical regimen, broken or actively inflamed skin); appropriate concomitant medication review including photosensitizers and other topical irritants; and a prescribed regimen consistent with the manufactured-product titration pattern unless the prescriber documents a patient-specific reason for variance [485146].

For modified-Kligman compounded creams, the pharmacist review additionally confirms the hydroquinone component strength (typically 4, 6%, avoiding higher long-term concentrations associated with exogenous ochronosis), corticosteroid potency appropriate to the treatment site and skin phototype, and a planned re-evaluation horizon (typically 8, 12 weeks of intensive use followed by intermittent maintenance) [161745]. RonanRx does not fill prescriptions for compounded tretinoin that read as routine substitution of compounded for manufactured product without documented clinical rationale, consistent with FDA guidance on compounded copies of commercially available drugs [54 52].

Quality and traceability

Active pharmaceutical ingredients are sourced from FDA-registered facilities with documented certificates of analysis. Each batch is recorded with lot numbers traceable to API source, compounding date, beyond-

use date, and dispensing pharmacist of record. Finished product lot records are retained per state board of pharmacy retention requirements.

Cold chain

Topical tretinoin preparations are stored at controlled room temperature and do not require cold-chain shipping. Shipments are protected from excessive heat (above 30°C / 86°F) during transit, and patients are advised to store the product at room temperature in a closed container away from direct sunlight. Tretinoin is photolabile; opaque or light-resistant tubes and jars are standard for both manufactured and compounded preparations [4][8][5][15][5].

Frequently Asked Questions About Topical Tretinoin

Is compounded tretinoin the same as Retin-A or Renova?

No. Retin-A, Renova, Retin-A Micro, Avita, Atralin, Altreno, and Tri-Luma are FDA-approved manufactured products. Compounded tretinoin is pharmacy-prepared on a patient-specific prescription and is not bioequivalent to any of the manufactured products [4][8][4][9]. Compounded drugs are not FDA-approved [5][3].

When is compounded tretinoin appropriate instead of a manufactured product?

Per FDA guidance, a compounded version of an FDA-approved drug requires a documented patient-specific clinical need that the manufactured product cannot meet, for example, an intermediate strength that no manufacturer makes (0.0125%, 0.075%, 0.15%), a vehicle without a specific allergen, or a multi-ingredient preparation like a modified-Kligman melasma cream that does not exactly match Tri-Luma's fixed concentrations [5][4][5][2]. Cost or preference does not qualify under section 503A.

What is the 'Kligman formula' and is it still used?

The original Kligman formula was published in Archives of Dermatology in 1975 by Kligman, Willis, and Pathak and combined tretinoin 0.1%, hydroquinone 5%, and dexamethasone 0.1% for hyperpigmentation [1][5]. Modified-Kligman compounded creams have remained the gold-standard topical regimen for melasma and post-inflammatory hyperpigmentation for half a century [1][6][1][4]. The FDA-approved Tri-Luma combination (fluocinolone 0.01% + hydroquinone 4% + tretinoin 0.05%) is the single commercially available product in this family; compounded modified-Kligman creams provide the flexibility to tailor each component when Tri-Luma's fixed strengths are not appropriate [1][7].

Why does my skin get worse before it gets better?

The first 2, 6 weeks of tretinoin therapy commonly produce a 'retinoid dermatitis' window, redness, peeling, dryness, burning, and a transient flare of acne lesions as pre-existing closed comedones surface [1][1][3][9]. This is

an adaptation pattern, not a sign to stop therapy. If irritation is intolerable, reduce frequency to every other or every third night, use a bland moisturizer underneath the tretinoin, and discuss with your prescriber before discontinuing [44].

How much improvement should I expect for photoaging?

In the Weiss 1988 double-blind trial in JAMA [2] and the Olsen 1992 emollient-cream pivotal trial [4], statistically significant improvement in fine wrinkles, mottled hyperpigmentation, and skin texture was observed at 16, 24 weeks; the Ellis 1990 extension [3] documented continued improvement out to 22 months. Patient-perceived results typically emerge between week 12 and week 24 and continue with sustained daily use. Tretinoin does not erase deep wrinkles or sun-induced skin laxity that involves the underlying connective tissue and fat compartment.

Why does the prescription have hydroquinone now when it used to be over-the-counter?

The September 2020 CARES Act amendments to the OTC monograph system removed hydroquinone from over-the-counter sale entirely. Hydroquinone is now available only by prescription, in the FDA-approved Tri-Luma combination cream and in compounded modified-Kligman preparations [52]. This regulatory change makes the prescribed compounded modified-Kligman cream a more central clinical option than it was a decade ago because patients can no longer self-treat with over-the-counter hydroquinone.

Can I use tretinoin during pregnancy?

Topical tretinoin is not recommended during pregnancy. Systemic absorption from topical application is low and epidemiologic studies have not established a malformation signal with topical tretinoin specifically, but the related oral retinoid isotretinoin is a known potent human teratogen and all FDA-approved topical tretinoin labels recommend discontinuation during pregnancy as a conservative measure [48495 1]. Discontinue prior to a planned pregnancy.

Does RonanRx sell compounded tretinoin directly to patients?

No. Compounded topical tretinoin requires a patient-specific prescription written by a licensed doctor for an identified patient with a documented clinical reason that no FDA-approved manufactured product (Retin-A, Retin-A Micro, Renova, Avita, Atralin, Altreno, Tri-Luma) is appropriate, plus pharmacist review before dispensing [54]. RonanRx is not a direct-to-consumer storefront [53].

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How to Access Topical Tretinoin

Compounded Topical Tretinoin is dispensed under 503A on a patient-specific prescription. Depending on your role, the next step looks different.

FOR PRESCRIBING CLINICIANS

Offer this medication

A pharmacist will follow up within two business days. We'll cover state availability, supported formulations, and what integration looks like for your clinic.

ronanrx.com/request-partnership-call

PATIENT WITH A DOCTOR

Receive your prescription

If your doctor has prescribed Topical Tretinoin, sign up so we can prepare and ship your medication. The signup wizard collects intake and connects you to the prescribing workflow.

ronanrx.com/patients

PATIENT WITHOUT A DOCTOR

Find a partner clinic

Partner clinicians prescribe through the RonanRx platform. Prescriptions are not initiated on this site. Read how the referral process works and how to find a partner clinic in your state.

ronanrx.com/find-clinic

Other compounds in the catalog

This monograph is one of many in the medication catalog. Compounds below are dispensed only on patient-specific prescriptions when appropriate. Browse the full catalog at ronanrx.com/medications and ronanrx.com/peptides, or scan the codes at right for each index.

Medications

Peptides

MEDICATIONS (42)

Alpha-Lipoic Acid (ALA) — Antioxidant & mitochondrial
Coenzyme Q10 (CoQ10) — Antioxidant & mitochondrial
Glutathione — Antioxidant & mitochondrial
Methylene Blue — Antioxidant & mitochondrial
NAD+ / NMN — Antioxidant & mitochondrial
Compounded Topical Anesthetics (BLT, LET) — Dermatology
Topical Minoxidil — Dermatology
Topical Tretinoin — Dermatology
Compounded Magnesium — Energy & nutritional
Cyanocobalamin — Energy & nutritional
High-Dose Vitamin D — Energy & nutritional
Hydroxocobalamin — Energy & nutritional
Iron (Compounded) — Energy & nutritional
L-Carnitine — Energy & nutritional
Methylcobalamin (B12) — Energy & nutritional
Methylfolate — Energy & nutritional
Anastrozole — Hormone optimization
Clomiphene & Enclomiphene — Hormone optimization
DHEA — Hormone optimization
Estradiol — Hormone optimization
Estriol — Hormone optimization
Human Chorionic Gonadotropin (HCG) — Hormone optimization
Oxytocin — Hormone optimization
Pregnenolone — Hormone optimization
Progesterone — Hormone optimization
Testosterone — Hormone optimization
Compounded Metformin — Metabolic & weight
Compounded Semaglutide — Metabolic & weight
Compounded Tirzepatide — Metabolic & weight
Lipotropic Injection (MIC, MICC) — Metabolic & weight
Low-Dose Naltrexone (LDN) — Metabolic & weight
Naltrexone-Bupropion Combination — Metabolic & weight
Topiramate — Metabolic & weight
Bremelanotide / PT-141 — Sexual health
Compounded Sildenafil — Sexual health
Compounded Tadalafil — Sexual health
Trimix Injection — Sexual health
Compounded Gabapentin — Sleep & recovery
Compounded Melatonin — Sleep & recovery
Compounded T3 (Liothyronine) — Thyroid
Compounded T3/T4 Combinations — Thyroid
Compounded T4 (Levothyroxine) — Thyroid

PEPTIDES (21)

Sermorelin — Available now

Tesamorelin — Available now

AOD-9604 — Growth-hormone axis (under FDA review)

CJC-1295 — Growth-hormone axis (under FDA review)

GHRP-2 / GHRP-6 — Growth-hormone axis (under FDA review)

Hexarelin — Growth-hormone axis (under FDA review)

Ipamorelin — Growth-hormone axis (under FDA review)

MK-677 / Ibutamoren — Growth-hormone axis (under FDA review)

5-Amino 1MQ — Metabolic & longevity (under FDA review)

Epitalon / Epithalon — Metabolic & longevity (under FDA review)

MOTS-C — Metabolic & longevity (under FDA review)

Thymosin Alpha-1 / Thymalin — Metabolic & longevity (under FDA review)

DSIP, Delta Sleep-Inducing Peptide — Neuro & cognitive (under FDA review)

Selank — Neuro & cognitive (under FDA review)

Semax — Neuro & cognitive (under FDA review)

Vasoactive Intestinal Peptide (VIP) — Neuro & cognitive (under FDA review)

BPC-157 — Tissue repair (under FDA review)

KPV — Tissue repair (under FDA review)

LL-37 — Tissue repair (under FDA review)

Pentadeca Arginate (PDA) — Tissue repair (under FDA review)

TB-500 / Thymosin Beta-4 — Tissue repair (under FDA review)