

## RESEARCH MONOGRAPH . COMPOUND PROFILE

# Stemoxydine

*A synthetic pyridinedicarboxylate ester developed by L'Oreal Research and Innovation as a topical hypoxia-mimetic agent that stabilizes HIF-1 alpha in perifollicular tissue, shortens the kenogen latency phase of the hair cycle, and increases visible scalp hair density through reactivation of dormant follicles.*

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## ABSTRACT

Stemoxydine (diethyl pyridine-2,4-dicarboxylate; CAS 41438-38-4) is a cell-permeable, competitive inhibitor of the 2-oxoglutarate- and iron(II)-dependent enzyme prolyl-4-hydroxylase (P4H, also designated HIF-PHD or EGLN), developed by L'Oreal Research and Innovation as a topical cosmetic active for the promotion of visible scalp hair density. The compound belongs to the pyridinedicarboxylate structural class, a group of 2-oxoglutarate analogs that occupy the cosubstrate-binding pocket of P4H isoforms and chelate the catalytic iron center, thereby preventing the oxygen-dependent hydroxylation of proline residues 402 and 564 on the alpha subunit of hypoxia-inducible factor 1 (HIF-1 alpha). Pharmacological inactivation of P4H results in constitutive stabilization of HIF-1 alpha under normoxic conditions, mimicking the transcriptional program of cellular hypoxia without actual oxygen deprivation. In the hair follicle, this hypoxia-mimetic signaling activates a downstream cascade that includes upregulation of vascular endothelial growth factor (VEGF), BNIP3, EGLN3, and carbonic anhydrase IX (CA9), genes whose expression profiles in stemoxydine-treated follicles cultured under normoxia closely mirror those of follicles cultured under true hypoxic conditions.

The principal biological effect of topical stemoxydine at the 5% concentration used in vehicle-controlled clinical studies is the shortening of the kenogen phase, the interval between telogen hair shedding and subsequent anagen reinitiation during which the follicle remains visibly empty. By reducing this latency period, stemoxydine increases the proportion of follicles bearing a visible

hair shaft at any given time, producing a measurable increase in scalp hair density without altering the intrinsic rate of hair shaft elongation or the duration of anagen itself. Three vehicle-controlled studies conducted by L'Oreal in male volunteers demonstrated statistically significant increases in hair density: a pilot study of 16 men showed a 4.5% density increase versus a 0.3% decrease with vehicle ( $p = 0.04$ ); a second study of 23 men showed an 11% increase versus 7% with vehicle ( $p = 0.029$ ); and a pivotal study of 100 men showed an 8% increase versus 4% with vehicle ( $p = 0.036$ ), corresponding to an estimated 1,700 additional visible hairs over 90 days of once-daily application. A subsequent randomized study in 79 female volunteers (Juchaux et al. 2020) demonstrated that a formulation combining 5% stemoxydine with 0.25% resveratrol significantly increased hair density from 1.5 months of use, with the combination producing synergistic stabilization of HIF-1 alpha protein and enhanced expression of downstream target genes compared to either component alone.

Stemoxydine is not classified as a pharmaceutical agent in any jurisdiction and has not received regulatory approval from the United States Food and Drug Administration or any equivalent authority for the treatment of androgenetic alopecia or any other medical condition. It is marketed exclusively as a cosmetic ingredient under L'Oreal brand names (Neogenic, Serioxyl, Serioxyl Advanced Denser Hair) and is available in research-grade form as diethyl pyridine-2,4-dicarboxylate from multiple chemical suppliers. The compound is generally well tolerated in topical application at the 5% concentration, with no skin intolerance recorded in vehicle-controlled trials. The safety profile beyond short-term topical use has not been characterized in peer-reviewed literature, and independent clinical validation outside of manufacturer-sponsored studies remains limited. This

monograph reviews the chemistry, molecular pharmacology, pharmacokinetics, preclinical biology, clinical evidence, sourcing, handling, stack-interaction considerations, adverse-event profile, and a comparative assessment of five topical hair density agents against stemoxydine on five competency standards.

# 1. Compound Identification

## 1.1 Names, synonyms, and registry identifiers

**Trade name:** Stemoxydine (registered trademark of L'Oreal S.A.).

**Chemical name (IUPAC):** Diethyl pyridine-2,4-dicarboxylate.

**Common synonyms:** 2,4-Diethylpyridine dicarboxylate; diethyl 2,4-pyridinedicarboxylate; 2,4-DPD; DEPD; pyridine-2,4-dicarboxylic acid diethyl ester.

**Chemical Abstracts Service registry number:** 41438-38-4.

**Development context:** The compound was identified and characterized by L'Oreal Research and Innovation (Clichy, France) through a screening program for prolyl-4-hydroxylase inhibitors capable of inducing hypoxia-mimetic signaling in perifollicular tissue. The trade name Stemoxydine was coined for commercial deployment in the L'Oreal Professional and L'Oreal Paris product lines beginning in 2012 [1, 2].

## 1.2 Structural class and chemistry

Stemoxydine is a pyridinedicarboxylate diester, a member of the broader class of 2-oxoglutarate analogs that function as competitive inhibitors of Fe(II)- and 2-oxoglutarate-dependent dioxygenases. The structural class includes pyridine-2,4-dicarboxylic acid (the free acid parent), dimethyl pyridine-2,4-dicarboxylate, and fluorinated derivatives that have been investigated as inhibitors of collagen prolyl-4-hydroxylase, HIF-prolyl hydroxylase domain proteins (PHD1, PHD2, PHD3), and factor-inhibiting HIF (FIH) [3, 4]. The diethyl ester form confers cell permeability, allowing the compound to cross keratinocyte and dermal papilla cell membranes before intracellular ester hydrolysis liberates the active diacid at the enzymatic target site.

**Molecular formula:** C<sub>11</sub>H<sub>13</sub>NO<sub>4</sub>.

**Exact mass:** 223.0845 g/mol (monoisotopic).

**Molecular weight:** 223.23 g/mol.

**Physical properties:** Colorless to pale yellow liquid at room temperature. Boiling point approximately 78 degrees Celsius (at reduced pressure; decomposes at atmospheric boiling). Refractive index  $n_{20D}$  approximately 1.51. Soluble in water at approximately 1 mg/mL at 25 degrees Celsius, in ethanol at approximately 50 mg/mL, in dimethyl sulfoxide at approximately 20 mg/mL, and in dimethylformamide at approximately 30 mg/mL [5].

**Structural features:** The pyridine ring nitrogen and the two carboxylate groups at positions 2 and 4 are critical for pharmacological activity. The 2,4-dicarboxylate substitution pattern positions the two carbonyl oxygen atoms and the ring nitrogen to coordinate the catalytic Fe(II) center of prolyl hydroxylase in a geometry that mimics the binding mode of the natural cosubstrate 2-oxoglutarate. The ethyl ester groups serve as prodrug moieties; intracellular esterase-mediated hydrolysis generates the free diacid, which is the active enzyme inhibitor [3, 6].

## 1.3 Synthesis

Diethyl pyridine-2,4-dicarboxylate is prepared by Fischer esterification of commercially available pyridine-2,4-dicarboxylic acid (also known as lutidinic acid) with ethanol under acid catalysis. The reaction is typically conducted in refluxing ethanol with concentrated sulfuric acid or thionyl chloride as the activating agent, producing the diethyl ester in moderate to high yield (70 to 90 percent) after aqueous workup and distillation or column chromatography [7]. Alternative preparations employ carbodiimide-mediated coupling or acid chloride intermediates for selective mono- or diesterification. The compound is commercially available from multiple chemical suppliers (Santa Cruz Biotechnology, MedChemExpress, Sigma-Aldrich, Smolecule, Alfa Chemical) at greater than 98 percent purity by high-performance liquid chromatography, in quantities ranging from milligrams to kilograms [5, 8].

## 2. Abstract

Stemoxydine (diethyl pyridine-2,4-dicarboxylate; CAS 41438-38-4) is a synthetic, cell-permeable prolyl-4-hydroxylase (P4H) competitive inhibitor developed by L'Oreal Research and Innovation as a topical cosmetic active for increasing visible scalp hair density [1, 2]. The compound belongs to the 2-oxoglutarate analog structural class and functions by mimicking the natural cosubstrate of the Fe(II)- and 2-oxoglutarate-dependent prolyl hydroxylase domain enzymes (PHD1, PHD2, PHD3) that hydroxylate HIF-1 alpha, targeting it for von Hippel-Lindau-mediated proteasomal degradation under normoxic conditions [3, 6]. By competitively inhibiting this oxygen-sensing enzymatic step, stemoxydine stabilizes HIF-1 alpha protein in the absence of true hypoxia, activating the downstream transcriptional program of hypoxia-responsive genes including VEGF, BNIP3, EGLN3, and CA9 [9, 10].

Transcriptomic studies have demonstrated that treatment of human hair follicles with stemoxydine under normoxic conditions modifies gene expression in a pattern closely matching that of follicles cultured under hypoxic conditions [9]. At the biological level, hypoxia-mimetic signaling in the perifollicular niche maintains the immaturity and regenerative potential of outer root sheath keratinocyte stem cells, reduces colony-forming differentiation, and supports the transition from the kenogen latency phase to a new anagen growth phase [9, 11]. The net effect at the macroscopic level is a shortening of the kenogen phase, the empty-follicle interval between telogen shedding and the next anagen cycle, producing an increase in the number of follicles bearing a visible hair shaft at any given time.

Three vehicle-controlled clinical studies in male volunteers, each employing a 5% stemoxydine hydro-alcoholic lotion applied to the scalp, demonstrated statistically significant increases in hair density over 90 days of treatment, with the largest study (100 men) reporting an 8% increase in hair density versus 4% with vehicle ( $p = 0.036$ ), corresponding to approximately 1,700 additional visible hairs [9]. A randomized study of 79 female volunteers demonstrated that a 5% stemoxydine plus 0.25% resveratrol formulation significantly increased hair density from 1.5 months of use, with the antioxidant combination producing synergistic HIF-1 alpha stabilization in vitro [10]. A 2026 prospective trichoscopic evaluation by Elattar confirmed improvements in hair density parameters in androgenetic alopecia patients treated with topical stemoxydine [12].

The compound is not classified as a drug in any jurisdiction and carries no regulatory approval for the treatment of alopecia. It is marketed as a cosmetic ingredient in L'Oreal product lines (Neogenic, Serioxyl, Serioxyl Advanced) and is available as a research-grade chemical from multiple suppliers. Safety in short-term topical application appears favorable, with no skin intolerance recorded in controlled studies; long-term safety data and independent clinical replication outside manufacturer-sponsored research remain limited.

## 3. Discovery and Development History

### 3.1 Origin

The identification of stemoxydine arose from a research program at L'Oreal Research and Innovation (Clichy, France) initiated in the mid-2000s to identify small-molecule modulators of hair follicle stem cell biology. The program was motivated by the observation, reported by multiple groups studying hematopoietic and mesenchymal stem cell niches, that mild hypoxia (1 to 5 percent oxygen) promotes stem cell quiescence, preserves stemness markers, and enhances regenerative capacity [13]. L'Oreal researchers hypothesized that pharmacological simulation of hypoxic signaling in the perifollicular environment could maintain the regenerative competence of outer root sheath stem cells and reduce the duration of the kenogen phase, a poorly studied interval in the hair cycle during which the follicle remains visibly empty after telogen shedding and before the next anagen initiation [9, 14].

### 3.2 Screening and selection

The screening strategy targeted prolyl-4-hydroxylase (P4H), the oxygen-sensing enzyme that hydroxylates HIF-1 alpha at conserved proline residues and thereby directs it for ubiquitin-dependent proteasomal degradation. L'Oreal screened a library of 2-oxoglutarate analogs and related heterocyclic structures for competitive P4H inhibition, cell permeability in keratinocyte models, and the ability to induce a hypoxia-like transcriptional signature under normoxic conditions. Diethyl pyridine-2,4-dicarboxylate was selected as the lead compound on the basis of potent P4H competitive inhibition, favorable cell permeability as the diethyl ester pro-drug, and a clean transcriptomic profile in which the genes modified by stemoxydine treatment under normoxia closely matched those modified by true hypoxic culture conditions [9]. The compound was assigned the trade name Stemoxydine, reflecting the stem cell and oxygen-mimetic dimensions of the mechanism. The foundational patent estate was filed under L'Oreal ownership (European patent application No. EP 1 352 629 and subsequent filings) [15].

### 3.3 Product launch and commercialization

L'Oreal launched the first stemoxydine-containing product, Neogenic, in the L'Oreal Professional salon channel in 2012. The product contained 5% stemoxydine in a hydro-alcoholic lotion for daily scalp application, supplied in single-dose ampule format for 90-day treatment courses. The launch was supported by presentation of the three vehicle-controlled clinical studies (described in Section 7) at the European Hair Research Society meeting in 2012 and the World Congress of Hair Research in 2014 [9].

Subsequent product iterations incorporated a combination of stemoxydine with resveratrol (trans-3,5,4'-trihydroxystilbene), a polyphenolic antioxidant. This combination was commercialized as L'Oreal Serioxyl and subsequently as Serioxyl Advanced Denser Hair, positioned for both male and female consumers experiencing visible hair thinning. The formulation rationale for the stemoxydine-resveratrol combination was the demonstration by Juchaux et al. (2020) that resveratrol provides synergistic HIF-1 alpha stabilization through complementary antioxidant protection and that the combination upregulates downstream target gene expression more potently than either component alone [10, 16].

### 3.4 Current status

Stemoxydine remains a proprietary cosmetic active marketed exclusively through L'Oreal product lines. It has not been submitted for drug regulatory review in any jurisdiction and is not classified as a pharmaceutical agent. Independent academic investigation has been limited; the majority of published clinical and mechanistic data originate from L'Oreal-sponsored research. A 2026 prospective trichoscopic study by Elattar (Journal of Cosmetic Dermatology) represents the first independent clinical evaluation of topical stemoxydine for androgenetic alopecia in the peer-reviewed literature [12]. The compound is available as a research-grade chemical (diethyl pyridine-2,4-dicarboxylate, CAS 41438-38-4) from commercial suppliers, enabling independent laboratory investigation.

## 4. Mechanism of Action

### 4.1 The HIF-prolyl hydroxylase oxygen-sensing pathway

The molecular target of stemoxydine is the prolyl-4-hydroxylase domain (PHD) family of enzymes, also designated EGLN1 (PHD2), EGLN2 (PHD1), and EGLN3 (PHD3). These enzymes are Fe(II)- and 2-oxoglutarate-dependent dioxygenases that catalyze the hydroxylation of conserved proline residues (Pro-402 and Pro-564 in human HIF-1 alpha) within the oxygen-dependent degradation domain of the HIF-1 alpha subunit. Hydroxylation of these prolines creates a binding site for the von Hippel-Lindau (VHL) E3 ubiquitin ligase complex, which polyubiquitinates HIF-1 alpha and targets it for proteasomal degradation. Under normoxic conditions (approximately 21 percent oxygen), PHD enzymes are fully active, HIF-1 alpha is continuously hydroxylated and degraded, and HIF-1 alpha-dependent transcription is suppressed. Under hypoxic conditions (below approximately 5 percent oxygen), PHD activity is reduced by substrate (oxygen) limitation, HIF-1 alpha accumulates, dimerizes with HIF-1 beta (ARNT), translocates to the nucleus, and activates transcription of hypoxia-responsive element-containing genes including VEGF, erythropoietin, glucose transporter 1, BNIP3, EGLN3, and carbonic anhydrase IX [6, 17, 18].

### 4.2 Prolyl hydroxylase competitive inhibition by stemoxydine

Stemoxydine (as the intracellularly hydrolyzed free diacid, pyridine-2,4-dicarboxylic acid) is a competitive inhibitor of PHD enzymes at the 2-oxoglutarate co-substrate-binding site. The pyridine ring nitrogen and the two carboxylate groups at positions 2 and 4 coordinate the catalytic Fe(II) center in the enzyme active site in a geometry that mimics the bidentate coordination of 2-oxoglutarate. This dual interaction, combining cosubstrate-site occupancy with iron chelation, prevents the oxidative decarboxylation of 2-oxoglutarate and the coupled hydroxylation of HIF-1 alpha proline residues [3, 4, 6]. The inhibition is competitive with respect to 2-oxoglutarate, meaning that increasing concentrations of 2-oxoglutarate can overcome the inhibition, consistent with the structural mimicry mechanism.

The selectivity of pyridine-2,4-dicarboxylate for PHD isoforms over other 2-oxoglutarate-dependent dioxygenases (collagen prolyl-4-hydroxylase, lysyl hydroxylase, factor-inhibiting HIF) has been characterized in enzymatic assays. The compound inhibits all three PHD isoforms and also inhibits collagen prolyl-4-hydroxylase at comparable concentrations, a cross-reactivity that is shared across the pyridinedicarboxylate structural class [3, 19]. In the context of topical application to the scalp, the collagen P4H inhibition is not considered therapeutically limiting; collagen synthesis in the perifollicular dermis is not materially disrupted at the concentrations achieved by topical 5% formulations, and no clinical evidence of dermal collagen compromise has been reported.

## 4.3 HIF-1 alpha stabilization and downstream transcription

The functional consequence of PHD inhibition by stemoxydine is the stabilization of HIF-1 alpha protein under normoxic conditions. Western blot analyses of human keratinocytes treated with stemoxydine have demonstrated accumulation of HIF-1 alpha protein to levels comparable to those achieved by true hypoxic culture (1 percent oxygen) [9, 10]. Quantitative PCR analyses of downstream target gene expression have confirmed that stemoxydine treatment under normoxia upregulates BNIP3 (a mitophagy-associated BH3-only protein), EGLN3 (PHD3 itself, a negative-feedback component), and CA9 (carbonic anhydrase IX, a marker of HIF pathway activation) in the same direction and approximate magnitude as hypoxic culture [9].

The Juchaux et al. (2020) study further demonstrated that the combination of stemoxydine with resveratrol produced enhanced HIF-1 alpha protein stabilization compared to either agent alone in human keratinocyte cultures, and that the combination increased the expression of HIF-1 alpha target genes synergistically. The proposed mechanism for the synergy is that resveratrol provides antioxidant protection that preserves HIF-1 alpha protein from oxidative degradation pathways independent of the PHD-VHL axis, complementing the PHD-inhibitory activity of stemoxydine [10, 16].

## 4.4 Hair follicle biology and the kenogen phase

The hair follicle undergoes a cyclical process of growth (anagen, lasting 2 to 7 years in scalp follicles), regression (catagen, approximately 2 to 3 weeks), rest (telogen, approximately 2 to 4 months), and shedding (exogen). An additional phase, the kenogen, was described by Rebora and Guarrera (2002) as the interval between exogen shedding and the initiation of the next anagen cycle, during which the follicle remains visibly empty [14]. In healthy scalp, the kenogen phase is short (days to weeks) and affects a small proportion of follicles at any time. In hair thinning conditions, including age-related thinning and early androgenetic alopecia, the kenogen phase is prolonged, and the proportion of follicles in kenogen at any time increases, producing a visible reduction in hair density without a corresponding reduction in total follicle count [14, 20].

Stemoxydine acts as a kenogen phase shortener. By stabilizing HIF-1 alpha in the perifollicular niche, the compound activates VEGF-mediated angiogenesis and growth factor signaling that promotes the transition from the quiescent post-telogen state to a new anagen cycle. The HIF-1 alpha pathway is physiologically active in the dermal papilla during anagen, where perifollicular vascularization is maximal, and is downregulated during catagen and telogen [21, 22]. Pharmacological reactivation of the HIF pathway through PHD inhibition effectively recapitulates the pro-angiogenic and trichogenic signaling of the anagen-associated microenvironment, promoting follicle reactivation.

## 4.5 Effects on hair follicle stem cells

L'Oreal researchers measured the colony-forming efficiency (CFE) of keratinocytes derived from the outer root sheath (ORS) of human follicles cultured under normoxic (21 percent oxygen) or hypoxic (1 percent oxygen) conditions. Hypoxic culture reduced cell density and differentiation, suggesting maintenance of cell immaturity and stemness [9]. Treatment with stemoxydine under normoxic conditions produced a similar pattern of reduced differentiation and maintained regenerative potential, consistent with the interpretation that stemoxydine-mediated HIF-1 alpha stabilization preserves the stem cell compartment in a state of higher regenerative competence.

This stem cell maintenance effect is mechanistically coherent with the kenogen-shortening phenotype: follicles whose ORS stem cell populations maintain higher regenerative capacity are predicted to re-enter anagen more readily, reducing the

empty-follicle interval and increasing the proportion of density-contributing follicles at any given time.

## 5. Pharmacokinetics and Routes of Administration

### 5.1 Route of administration

Stemoxydine is administered exclusively by topical application to the scalp. The compound has not been studied by oral, intravenous, intramuscular, or subcutaneous routes in humans. The topical route is consistent with the intended cosmetic application and with the localization of the biological target (perifollicular P4H) in the scalp dermis and outer root sheath.

### 5.2 Percutaneous absorption

Stemoxydine is formulated as a 5% (weight/volume) solution in a hydro-alcoholic vehicle for scalp application. The ethanol component serves as a penetration enhancer, facilitating partitioning of the compound through the stratum corneum and into the follicular infundibulum. The compound is lipophilic (refractive index 1.51, moderate water solubility at 1 mg/mL), consistent with reasonable percutaneous penetration through hair follicle orifices and the intercellular lipid pathways of the stratum corneum [5].

Quantitative human skin penetration data (Franz diffusion cell or tape-stripping studies) have not been published in the peer-reviewed literature. The clinical efficacy observed in vehicle-controlled studies at the 5% concentration provides indirect evidence of sufficient penetration to achieve pharmacologically active concentrations in the perifollicular compartment.

### 5.3 Local metabolism

The diethyl ester form of stemoxydine is a prodrug. Intracellular esterases in keratinocytes, dermal papilla cells, and other perifollicular cell populations hydrolyze the ethyl ester groups to generate the free diacid (pyridine-2,4-dicarboxylic acid), which is the active P4H competitive inhibitor [3, 6]. The rate and completeness of intracellular hydrolysis have not been quantitatively characterized in human skin

cells in the published literature, but the pharmacological activity observed in keratinocyte culture systems and in clinical application confirms that hydrolysis occurs at a rate sufficient to produce functional P4H inhibition.

## 5.4 Systemic exposure

Systemic absorption and exposure data for topically applied stemoxydine have not been published. Given the molecular weight (223.23 g/mol), the moderate lipophilicity, and the topical application to a limited surface area of scalp skin, systemic exposure is expected to be low. The compound has no known systemic pharmacological targets at the concentrations predicted from topical scalp application, and no systemic adverse events have been reported in controlled studies.

## 5.5 Formulation considerations

Commercial stemoxydine products employ a hydro-alcoholic vehicle, typically containing ethanol at 40 to 60 percent and propylene glycol at 3 to 10 percent as co-solvents and penetration enhancers. The Serioxyl Advanced formulation additionally contains 0.25% resveratrol as a synergistic HIF-1 alpha stabilizer [10, 16]. Application is once daily to the scalp, with product instructions specifying massage into the scalp and no rinsing. Treatment courses of 90 days are recommended in commercial product labeling, consistent with the duration of the pivotal clinical studies.

## 6. Preclinical Pharmacology

### 6.1 In vitro P4H inhibition

Diethyl pyridine-2,4-dicarboxylate is characterized as a cell-permeable competitive inhibitor of the oxygen-sensing enzyme HIF prolyl hydroxylase [5, 6]. The parent compound class (pyridine-2,4-dicarboxylate and analogs) has been extensively studied in enzymatic assays against PHD2 (EGLN1), the principal isoform responsible for normoxic HIF-1 alpha degradation. Inhibition is competitive with respect to 2-oxoglutarate, with the pyridine nitrogen and C-2/C-4 carboxylates coordinating the active-site Fe(II) in a bidentate geometry that displaces the natural cosubstrate [3, 4]. Fluorinated derivatives of pyridine-2,4-dicarboxylate have been shown to be more potent inhibitors of human 2-oxoglutarate-dependent oxygenases, with selectivity patterns that vary across PHD isoforms, collagen P4H, FIH, and other family members [4].

### 6.2 HIF-1 alpha stabilization in cell culture

Western blot analyses in human keratinocyte (HaCaT) and primary outer root sheath keratinocyte cultures have demonstrated that stemoxydine at concentrations corresponding to the 5% topical formulation stabilizes HIF-1 alpha protein under normoxic (21 percent O<sub>2</sub>) conditions to levels comparable to true hypoxic (1 percent O<sub>2</sub>) culture [9, 10]. Quantitative PCR confirmation of downstream target gene induction (BNIP3, EGLN3, CA9) validates the functional competence of the stabilized HIF-1 alpha.

### 6.3 Outer root sheath stem cell biology

Colony-forming efficiency assays of ORS keratinocytes demonstrated that stemoxydine-treated cells cultured under normoxia showed reduced terminal differentiation and maintained regenerative capacity, a pattern consistent with preservation of stem cell immaturity [9]. This finding aligns with broader stem cell biology literature demonstrating that mild hypoxia (2 to 5 percent oxygen) maintains the undifferentiated state of multiple stem cell populations, including hematopoietic stem cells, mesenchymal stem cells, and neural progenitor cells [13].

## 6.4 Dermal papilla cell signaling

HIF-1 alpha is physiologically expressed in dermal papilla cells during the anagen phase and is associated with the pro-angiogenic, trichogenic signaling environment of the actively growing follicle [21, 22]. Suppression of EGLN1/3 (PHD1/3) expression in dermal papilla cells induces proliferation through the HIF-1 alpha to VEGF signaling cascade [22]. Stemoxydine, through PHD inhibition, recapitulates this pro-proliferative dermal papilla phenotype, supporting the mechanistic rationale for anagen reinduction and kenogen shortening.

## 6.5 Synergy with resveratrol

In vitro combination studies reported by Juchaux et al. (2020) demonstrated that co-treatment with stemoxydine and resveratrol produced greater HIF-1 alpha protein accumulation and greater downstream gene expression than either agent alone [10]. The proposed mechanism is dual-pathway stabilization: stemoxydine prevents PHD-mediated hydroxylation and VHL-dependent degradation, while resveratrol provides antioxidant protection against reactive oxygen species-mediated HIF-1 alpha degradation through oxygen-independent pathways. This synergy provided the scientific basis for the commercial Serioxyl Advanced formulation.

# 7. Clinical Evidence Base

## 7.1 L'Oreal vehicle-controlled studies in male volunteers

Three randomized, vehicle-controlled clinical studies conducted by L'Oreal Research and Innovation evaluated the efficacy of a 5% stemoxydine hydro-alcoholic lotion applied to the scalp of male volunteers experiencing visible hair thinning [9].

**Study 1a (pilot, n = 16 men):** Participants applied 5% stemoxydine lotion to the scalp 5 days per week for 90 days. Hair density, measured by phototrichogram in a defined scalp zone, increased by 4.5% in the stemoxydine group versus a decrease of 0.3% in the vehicle group ( $p = 0.04$ ). No skin intolerance was recorded in either group.

**Study 1b (n = 23 men):** Participants applied 5% stemoxydine lotion to the scalp 5 days per week for 90 days. Hair density increased by 11% in the stemoxydine group versus 7% in the vehicle group ( $p = 0.029$ ). The vehicle group increase in this study was higher than in Study 1a, attributed to variability in baseline thinning severity and seasonal hair cycling effects. The between-group difference remained statistically significant.

**Study 2 (pivotal, n = 100 men):** Participants applied 5% stemoxydine lotion to the scalp once daily for 90 days in a double-blind, vehicle-controlled design. Hair density increased by 8% in the stemoxydine group versus 4% in the vehicle group ( $p = 0.036$ ). The 4% net effect over vehicle corresponded to an estimated 1,700 additional visible hairs across the scalp. The study additionally demonstrated a significant decrease in the percentage of hair follicles in the kenogen phase in the stemoxydine group, consistent with the proposed mechanism of kenogen phase shortening [9].

These studies were presented at the European Hair Research Society meeting (2012) and the World Congress of Hair Research (2014) and are cited in the peer-reviewed literature, though the full study reports have not been published as independent peer-reviewed journal articles.

## 7.2 Stemoxydine-resveratrol combination in female volunteers

Juchaux et al. (2020) reported a randomized clinical trial in 79 Caucasian female volunteers aged 18 to 65 years evaluating a topical formulation containing 5% pyridine-2,4-dicarboxylic acid diethyl ester (stemoxydine) and 0.25% resveratrol [10]. The study combined in vitro mechanistic characterization (Western blot, qPCR, oxidative stress assays) with a clinical efficacy assessment. The treatment significantly increased hair density from 1.5 months of use. In vitro, the combination stabilized HIF-1 alpha protein and increased expression of downstream target genes synergistically compared to either component alone. The oxidative stress evaluation using the DCFH-DA probe in hair follicle cells demonstrated antioxidant activity of the resveratrol component, supporting the dual-pathway stabilization hypothesis. This study represents the first peer-reviewed publication of stemoxydine clinical efficacy data in a mainstream scientific journal (International Journal of Cosmetic Science) [10].

## 7.3 Independent trichoscopic evaluation in androgenetic alopecia

Elattar (2026) reported a prospective, pre-post, single-arm exploratory study evaluating the trichoscopic effectiveness of topical stemoxydine for hair restoration in androgenetic alopecia, published in the Journal of Cosmetic Dermatology [12]. This study represents the first independent (non-manufacturer-sponsored) clinical evaluation of stemoxydine in the peer-reviewed literature. The study employed trichoscopic quantification of hair density, follicular unit density, and hair caliber as outcome measures. Results confirmed improvements in hair density parameters consistent with the earlier L'Oreal-sponsored data, though the single-arm design and absence of a vehicle control group limit the strength of causal inference.

## 7.4 Serioxyl product studies

Additional clinical data have been generated in the context of L'Oreal product development studies for the Serioxyl and Serioxyl Advanced product lines. A study of 79 women aged 18 to 65 reported that 86% of participants perceived increased hair density after 6 weeks of use of the Serioxyl Advanced Denser Hair serum, with claims of more than 1,000 new hairs within 6 weeks and more than 1,600 new hairs at the end of the full treatment course [23]. These data are derived from product-

specific studies with cosmetic-grade endpoints (self-assessment, expert visual grading) rather than instrument-measured phototrichogram data, and should be interpreted in the context of cosmetic claim substantiation rather than pharmaceutical-grade clinical evidence.

## 7.5 Limitations of the clinical evidence

The clinical evidence base for stemoxydine has several important limitations that investigators should consider:

(a) The majority of controlled efficacy data originate from manufacturer-sponsored (L'Oreal) research, with inherent potential for sponsorship bias in study design, endpoint selection, and reporting.

(b) The largest vehicle-controlled study enrolled 100 participants and employed a 90-day treatment period. No large-scale (greater than 500 participant), long-duration (greater than 12 months), or dose-ranging studies have been published.

(c) No head-to-head comparative trial against an established hair loss treatment (minoxidil, finasteride) has been published in the peer-reviewed literature.

(d) The compound has not been evaluated in a regulatory drug-development framework with the associated requirements for Good Clinical Practice compliance, independent data monitoring, and standardized efficacy endpoints.

(e) Independent replication of the manufacturer-sponsored findings has been limited to the single-arm Elattar (2026) study, which lacked a vehicle control group.

## 8. Sourcing and Quality Verification

Stemoxydine is available through two principal channels: commercial cosmetic products and research-grade chemical supply.

**Commercial cosmetic products:** L'Oreal Professional Serioxyl Advanced Denser Hair serum (5% stemoxydine plus 0.25% resveratrol) and predecessor products (Neogenic, Serioxyl) are available through professional salon channels and authorized retail outlets. These products are manufactured under cosmetic Good Manufacturing Practice and are the highest-quality source for applications where cosmetic-grade material is appropriate. The stemoxydine concentration in commercial products is typically 5% weight/volume.

**Research-grade chemical supply:** Diethyl pyridine-2,4-dicarboxylate (CAS 41438-38-4) is available from Santa Cruz Biotechnology, MedChemExpress, Smolecule, Sigma-Aldrich, Alfa Chemical, and other suppliers at greater than 98% purity by HPLC. Supply is in milligram to gram quantities as a neat liquid. Pricing is moderate, in the range of \$30 to \$150 per 50 mg of research-grade material depending on supplier and quantity [5, 8].

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity (target: greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (224.09 [M+H]<sup>+</sup> for the protonated molecular ion)
- Nuclear magnetic resonance spectroscopy (<sup>1</sup>H and <sup>13</sup>C) confirmation of the pyridine-2,4-dicarboxylate diethyl ester structure
- Refractive index measurement (expected n<sub>20D</sub> approximately 1.51)
- Karl Fischer or loss-on-drying analysis for residual water content

Third-party analytical confirmation is recommended for any investigation where dose-response precision is important, as lot-to-lot variability in purity and residual solvent content may affect experimental reproducibility.

## 9. Reconstitution and Handling

Stemoxydine (diethyl pyridine-2,4-dicarboxylate) is supplied as a neat liquid at room temperature. For research applications, stock solutions are prepared by dilution in the appropriate solvent system.

**Recommended stock solutions:** Ethanol at 50 mg/mL; dimethyl sulfoxide at 20 mg/mL; dimethylformamide at 30 mg/mL; water at 1 mg/mL. For cell culture experiments, dimethyl sulfoxide stock solutions are diluted into culture medium to achieve final dimethyl sulfoxide concentrations below 0.1 percent to minimize vehicle cytotoxicity [5].

**Storage:** The neat liquid and stock solutions should be stored at minus 20 degrees Celsius. The compound is stable at refrigerated conditions (2 to 8 degrees Celsius) for short-term storage. Light protection is reasonable practice but has not been demonstrated to be critical for compound stability. Avoid repeated freeze-thaw cycles; aliquoting of stock solutions for single-use is recommended.

**Topical formulation for investigational use:** Investigators preparing topical formulations for scalp application should dissolve stemoxydine at 5 percent weight/volume in a hydro-alcoholic vehicle (typically 40 to 60 percent ethanol, 3 to 10 percent propylene glycol, balance purified water), consistent with the formulation approach used in the vehicle-controlled clinical studies [9, 10]. The hydro-alcoholic vehicle serves as a penetration enhancer and ensures uniform distribution on the scalp. Prepared topical formulations should be used within 30 days and stored at room temperature (15 to 25 degrees Celsius) protected from direct sunlight.

**Compatibility:** The compound is compatible with standard laboratory plasticware (polypropylene, polystyrene) and glassware. No specific incompatibilities with common excipients have been reported. When formulated with resveratrol, the antioxidant should be dissolved separately and combined with the stemoxydine solution to avoid potential redox interactions during preparation [10].

## 10. Stack Interactions and Combinations

Stemoxydine is a topical cosmetic active without systemic pharmacological activity at the concentrations achieved by scalp application. Stack interactions are therefore principally local (topical co-application) rather than systemic (drug-drug interaction).

**Resveratrol:** The combination of 5% stemoxydine with 0.25% resveratrol has been characterized as synergistic for HIF-1 alpha stabilization and hair density improvement [10, 16]. This combination is the basis of the commercial Serioxyl Advanced formulation and represents the best-characterized stemoxydine combination in the literature. The synergy is mechanistically coherent (dual-pathway HIF-1 alpha stabilization through PHD inhibition and antioxidant protection) and clinically supported.

**Minoxidil:** Concurrent topical application of stemoxydine and minoxidil has not been evaluated in controlled studies. The mechanisms are non-overlapping: stemoxydine inhibits P4H to stabilize HIF-1 alpha, while minoxidil acts as a potassium channel opener (K-ATP) with secondary VEGF-inducing activity that may be partly HIF-1 alpha-mediated [24, 25]. The theoretical interaction is additive or synergistic, as the two compounds converge on VEGF-mediated perifollicular angiogenesis through distinct upstream mechanisms. The practical consideration is that both agents are typically formulated in hydro-alcoholic vehicles, and co-application may increase scalp dryness and irritation from cumulative alcohol and propylene glycol exposure.

**Aminexil (diaminopyrimidine oxide):** Aminexil is a second L'Oreal-developed topical hair loss active that acts as a lysyl hydroxylase inhibitor, reducing perifollicular collagen cross-linking and fibrosis [26]. The mechanisms of stemoxydine (P4H inhibition, HIF-1 alpha stabilization) and aminexil (lysyl hydroxylase inhibition, anti-fibrotic) are non-overlapping and complementary. No controlled combination data have been published.

**Finasteride (oral):** The systemic 5-alpha-reductase inhibitor finasteride acts through hormonal modulation (reduction of dihydrotestosterone), a mechanism entirely distinct from the topical HIF-1 alpha stabilization of stemoxydine. No pharmacokinetic interaction is expected. The combination of topical stemoxydine with oral finasteride is theoretically additive, addressing hair loss through complementary mechanisms (hormonal and follicular stem cell), and is a rational combination for research investigation.

**Other topical actives:** Co-application with ketoconazole shampoo, caffeine-containing topical preparations, saw palmetto extracts, or other cosmetic hair density actives has not been formally evaluated. No specific contraindications or antagonistic interactions are predicted from the known mechanisms.

**Systemic medications:** No systemic drug interactions are expected or have been reported for topical stemoxydine at the 5% concentration, given the anticipated low systemic absorption. Investigators should note that systemic prolyl hydroxylase inhibitors (roxadustat, daprodustat, vadadustat, molidustat), which are approved or in development for the treatment of anemia of chronic kidney disease through systemic HIF-1 alpha stabilization and erythropoietin induction, share the same molecular target [27]. Concurrent use of topical stemoxydine with systemic PHD inhibitors has not been studied but is unlikely to produce clinically meaningful additive systemic HIF-1 alpha stabilization given the topical route and limited systemic absorption.

# 11. Adverse Events and Safety

## 11.1 Controlled study safety data

Vehicle-controlled clinical studies of 5% stemoxydine hydro-alcoholic lotion applied to the scalp for 90 days in male volunteers reported no recorded skin intolerance in either the stemoxydine or vehicle groups [9]. The Juchaux et al. (2020) study in 79 female volunteers similarly reported no significant adverse events attributable to the stemoxydine-resveratrol formulation [10].

## 11.2 Commonly reported user experiences

Post-market user reports from commercial stemoxydine products (Neogenic, Serioxyl) include:

- Mild scalp irritation (itching, redness, tingling) at the application site, particularly during the first days of use. This is attributed principally to the hydro-alcoholic vehicle (ethanol and propylene glycol) rather than to stemoxydine itself, as similar symptoms occur with vehicle-only application.
- Scalp dryness or flaking, associated with the high ethanol content of the formulation.
- Temporary increase in hair shedding during the first 2 to 4 weeks of use, consistent with a telogen effluvium-like shedding phase as dormant follicles are stimulated to re-enter anagen (a phenomenon also observed with minoxidil initiation).

## 11.3 Theoretical safety considerations

**Collagen P4H cross-reactivity:** Pyridine-2,4-dicarboxylate inhibits collagen prolyl-4-hydroxylase as well as HIF-PHD at comparable concentrations [3, 19]. Collagen P4H is essential for the post-translational hydroxylation of proline residues in collagen triple-helix domains, a requirement for collagen thermal stability and secretion. Chronic inhibition of dermal collagen P4H could theoretically impair collagen synthesis and dermal structural integrity. No clinical evidence of dermal collagen

compromise has been reported at the 5% topical concentration over 90-day treatment courses, but the possibility warrants monitoring in longer-duration applications.

**Systemic HIF-1 alpha stabilization:** Systemic PHD inhibitors produce erythropoietin induction, polycythemia, and potentially promote angiogenesis in unintended tissues [27]. These concerns are not relevant to topical stemoxydine at the 5% concentration given the low predicted systemic exposure, but would become relevant if the compound were administered by systemic routes or at substantially higher topical concentrations.

**Long-term safety:** No long-term (greater than 12 months) safety data have been published for topical stemoxydine. The compound is classified as a cosmetic ingredient and has not undergone the chronic toxicology, genotoxicity, carcinogenicity, and reproductive toxicology testing required for pharmaceutical drug approval.

## 11.4 Regulatory classification

Stemoxydine is classified as a cosmetic ingredient, not a drug, in all jurisdictions where it is marketed. It has not been evaluated by the United States Food and Drug Administration, the European Medicines Agency, or any equivalent regulatory authority as a treatment for androgenetic alopecia or any medical condition. The cosmetic classification reflects both the intended use (increasing visible hair density through cosmetic modification of the hair cycle) and the regulatory strategy of the manufacturer (L'Oreal), and does not constitute a determination of safety or efficacy to pharmaceutical standards.

## 12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five topical or dermatological hair density agents against stemoxydine, evaluated on five competency standards: novelty, effect size, promising potential (current development state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal agents with substantive clinical evidence or commercial presence in the topical hair density space, with priority on those that address follicular biology rather than hormonal mechanisms.

### 12.1 Minoxidil

**Mechanism:** Potassium channel opener (K-ATP channel agonist) with secondary effects including VEGF induction, prostaglandin E2 synthesis, Wnt/beta-catenin pathway modulation, and stimulation of dermal papilla cell proliferation. The precise mechanism of hair growth promotion remains incompletely characterized despite decades of clinical use [24, 25].

**Regulatory status:** FDA-approved (1988 for topical 2%; 1993 for topical 5%) for the treatment of androgenetic alopecia in both men and women. The only topical hair loss agent with full regulatory approval in the United States.

**Novelty:** Low. Minoxidil has been in clinical use for hair loss since the late 1980s and is the reference standard for the field. The mechanism, while incompletely understood, is well characterized at the pathway level.

**Effect size:** Moderate to large. Pivotal trials demonstrated a 12 to 18% increase in non-vellus hair count at the vertex over 48 weeks with 5% topical minoxidil versus placebo [28]. Effect size is substantially larger than the 4% net effect over vehicle reported for stemoxydine in the 100-man study. Meta-analyses consistently support minoxidil efficacy with moderate effect sizes (Cohen's d approximately 0.5 to 0.8 for hair count endpoints).

**Promising potential:** Established. Minoxidil is the gold standard for topical hair loss treatment, with continuous commercial availability, extensive generic competition, and ongoing reformulation innovation (oral low-dose minoxidil, foam formulations, combination products).

**Side-effect profile:** Moderate. Common adverse events include scalp irritation (particularly with propylene glycol-containing solutions), hypertrichosis (unwanted facial hair growth in women), initial telogen effluvium, and contact dermatitis. Rare systemic effects (tachycardia, fluid retention, hypotension) are reported principally with oral minoxidil use. The safety profile is well characterized over decades of post-market surveillance.

**Overall validation:** Very high. Minoxidil has the most extensive clinical evidence base of any topical hair loss agent, with FDA approval, multiple large-scale randomized controlled trials, and decades of post-market safety data.

**Comparison to stemoxydine:** Minoxidil produces a substantially larger effect on hair density (12 to 18% increase versus 4% net effect for stemoxydine), has full regulatory approval, and has an extensive safety database. Stemoxydine has the advantages of a cleaner side-effect profile (no hypertrichosis, no cardiovascular effects), a well-defined molecular target (P4H), and a complementary mechanism that could theoretically be combined with minoxidil for additive benefit.

## 12.2 Aminexil (diaminopyrimidine oxide, 2,4-diamino-6-piperidinopyrimidine 3-oxide)

**Mechanism:** Lysyl hydroxylase inhibitor. Aminexil inhibits the cross-linking enzyme lysyl hydroxylase, reducing perifollicular collagen rigidification and fibrosis that can constrict the follicular sheath and impair follicle cycling [26]. The anti-fibrotic mechanism is distinct from the HIF-stabilizing mechanism of stemoxydine and the vasodilatory mechanism of minoxidil.

**Regulatory status:** Cosmetic ingredient (L'Oreal). Not approved as a drug in any jurisdiction.

**Novelty:** Low. The compound has been commercially available since the late 1990s (L'Oreal Dercos) and is structurally related to minoxidil (a pyrimidine derivative with the piperidinyl group removed).

**Effect size:** Small. Published data suggest modest reductions in hair loss rate but minimal hair regrowth. Direct comparative data with stemoxydine are not available. The manufacturer (L'Oreal) has deprioritized aminexil in favor of stemoxydine in its product portfolio, and aminexil is increasingly rare as a standalone active.

**Promising potential:** Low. The compound is commercially marginalized, with few current products containing aminexil as a primary active. L'Oreal has shifted its hair density platform to stemoxydine-based formulations.

**Side-effect profile:** Favorable. Mild scalp irritation is the principal reported adverse event, consistent with vehicle effects.

**Overall validation:** Low to moderate. Clinical data are limited and largely manufacturer-sponsored. No large-scale randomized controlled trials have been published in the peer-reviewed literature.

**Comparison to stemoxydine:** Aminexil and stemoxydine are both L'Oreal-developed cosmetic actives targeting distinct aspects of follicular biology (anti-fibrotic versus hypoxia-mimetic). Stemoxydine has a better-defined molecular target, a larger clinical evidence base, and is the current focus of L'Oreal's hair density product development. The mechanisms are complementary and could theoretically be combined.

## 12.3 Finasteride (oral)

**Mechanism:** Competitive inhibitor of type II 5-alpha-reductase, reducing the conversion of testosterone to dihydrotestosterone (DHT) in the prostate and hair follicle. DHT is the principal androgen mediating follicular miniaturization in androgenetic alopecia [29].

**Regulatory status:** FDA-approved (1997) for male-pattern hair loss at 1 mg oral daily dose. Not approved for women.

**Novelty:** Low. The compound has been in clinical use for hair loss for nearly three decades. The hormonal mechanism is well established.

**Effect size:** Large. Pivotal trials demonstrated significant increases in hair count (approximately 10 to 15% increase over 12 months), reduction in progressive hair loss, and in some patients, visible regrowth. Effect size is larger than stemoxydine

and comparable to or greater than topical minoxidil [29, 30].

**Promising potential:** Established. Finasteride remains a first-line treatment for male androgenetic alopecia, with extensive clinical experience and generic availability. Topical finasteride formulations are under active development to reduce systemic exposure.

**Side-effect profile:** Moderate to significant. Reported adverse events include decreased libido, erectile dysfunction, and decreased ejaculate volume (occurring in 1 to 5% of users in controlled trials). Rare reports of persistent sexual dysfunction after discontinuation (post-finasteride syndrome) have generated significant concern, though causality remains debated [31]. The compound is teratogenic (FDA category X) and is contraindicated in women of childbearing potential.

**Overall validation:** Very high. FDA-approved, multiple large-scale RCTs, decades of post-market experience, well-characterized mechanism.

**Comparison to stemoxydine:** Finasteride operates through an entirely different mechanism (hormonal) and route (systemic oral) compared to the topical PHD-inhibiting activity of stemoxydine. Finasteride produces a larger effect size but carries a more significant adverse-event profile, including sexual side effects and teratogenicity that are absent from the stemoxydine safety profile. The two agents could be rationally combined for complementary mechanistic coverage.

## 12.4 Redensyl (dihydroquercetin-glucoside plus EGCG2 plus glycine)

**Mechanism:** A proprietary combination ingredient (Induchem/Givaudan) containing dihydroquercetin-glucoside (DHQG), which targets hair follicle stem cells in the bulge region through activation of the Wnt signaling pathway and promotion of outer root sheath stem cell proliferation [32]. The combination also contains epigallocatechin gallate glucoside (EGCG2) and glycine as supporting actives.

**Regulatory status:** Cosmetic ingredient. Not approved as a drug in any jurisdiction.

**Novelty:** Moderate. The Wnt-pathway targeting of bulge stem cells represents a mechanism distinct from the P4H-inhibiting activity of stemoxydine and the vasodilatory mechanism of minoxidil.

**Effect size:** Moderate (manufacturer-sponsored data). A 90-day study reported a 17% increase in anagen hair count versus a 2% increase with placebo, and a 9% reduction in telogen hair count [32]. These data have not been independently replicated in peer-reviewed controlled trials.

**Promising potential:** Moderate. Redensyl is commercially successful as a cosmetic ingredient in multiple third-party formulations. Independent clinical validation is limited.

**Side-effect profile:** Favorable. No significant adverse events reported in manufacturer studies.

**Overall validation:** Low to moderate. Clinical evidence is limited to manufacturer-sponsored studies. No regulatory-grade clinical trials have been conducted.

**Comparison to stemoxydine:** Redensyl and stemoxydine both target hair follicle stem cell biology through distinct molecular mechanisms (Wnt pathway versus HIF-1 alpha pathway). Both are cosmetic ingredients with limited independent clinical validation. Redensyl's reported effect size on anagen hair count (17% increase) is larger than stemoxydine's reported density effect (4 to 8% increase), though the studies differ in design, endpoints, and rigor. The two agents target complementary pathways and could theoretically be combined.

## 12.5 Kopexil (stemoxydine structural analog)

**Mechanism:** Kopexil is a proprietary L'Oreal active structurally related to stemoxydine (a pyridinedicarboxylate derivative) with an anti-hair loss positioning. The precise mechanism has been described as anti-adhesion at the perifollicular matrix level, reducing the collagen anchoring rigidity that may impair follicle cycling, though the molecular target has not been as precisely characterized as stemoxydine's P4H inhibition [33].

**Regulatory status:** Cosmetic ingredient (L'Oreal).

**Novelty:** Low to moderate. Kopexil is a structural evolution within L'Oreal's pyridinedicarboxylate platform but has not been as extensively characterized in the scientific literature as stemoxydine.

**Effect size:** Small to moderate. Manufacturer-sponsored data claim reductions in hair loss rate and improvements in hair anchoring force, but controlled hair density data comparable to the stemoxydine phototrichogram studies have not been published.

**Promising potential:** Moderate. Kopexil is included in current L'Oreal Elvive product lines, positioning it as a mass-market companion to the professional-channel stemoxydine formulations.

**Side-effect profile:** Favorable. No significant adverse events reported.

**Overall validation:** Low. Published scientific evidence is minimal. The compound is positioned primarily on manufacturer claims rather than peer-reviewed clinical data.

**Comparison to stemoxydine:** Kopexil and stemoxydine are both L'Oreal pyridinedicarboxylate platform compounds. Stemoxydine has a substantially better-characterized mechanism (P4H competitive inhibition, HIF-1 alpha stabilization), a larger clinical evidence base (three vehicle-controlled studies, one peer-reviewed journal publication), and greater research-community recognition. Kopexil appears to be a mass-market positioning variant rather than a mechanistically distinct agent.

## 12.6 Comparator summary

The five comparator compounds occupy distinct positions in the topical hair density landscape. **Minoxidil** is the regulatory and clinical gold standard with the largest effect size and the most extensive safety database; its principal limitation is the side-effect profile (hypertrichosis, cardiovascular effects, contact dermatitis). **Aminexil** is a historically significant but commercially declining L'Oreal active with a small effect size and limited current relevance. **Finasteride** produces the largest effect size among the comparators but operates through a systemic hormonal mechanism with a significant adverse-event burden and is restricted to male use. **Redensyl** is a commercially successful cosmetic ingredient with a distinct stem cell mechanism (Wnt pathway) but limited independent clinical validation. **Kopexil** is a structural relative of stemoxydine with minimal published scientific evidence.

Stemoxydine occupies a unique position in this landscape: it has the best-characterized molecular mechanism of any cosmetic hair density active (P4H competitive inhibition leading to HIF-1 alpha stabilization), a coherent biological rationale (hy-

poxia-mimetic signaling maintaining follicular stem cell competence and shortening the kenogen phase), a favorable safety profile relative to the pharmaceutical comparators (minoxidil and finasteride), and a peer-reviewed scientific literature that, while limited, exceeds that of most cosmetic competitors (aminexil, Redensyl, Kopexil). Its principal limitation is the modest effect size (4 to 8% hair density increase over vehicle in 90 days), which is substantially smaller than minoxidil (12 to 18%) and finasteride (10 to 15%) and positions the compound as a cosmetic density enhancer rather than a pharmaceutical hair loss treatment. The absence of independent clinical replication, the lack of head-to-head trials against established treatments, and the reliance on manufacturer-sponsored data further limit the evidentiary weight of the current clinical record.

Investigators considering stemoxydine for hair biology research should value its well-defined molecular target and mechanism, its utility as a tool compound for studying HIF-1 alpha signaling in the follicular niche, and its potential for rational combination with mechanistically complementary agents (minoxidil, finasteride, Redensyl). Clinical translation expectations should be calibrated to the modest effect size and limited independent validation available in the current evidence base.

## 13. References

1. L'Oreal Research and Innovation. Stemoxydine: a new molecular approach to hair density. Internal communication and European Hair Research Society Presentation, 2012.
2. L'Oreal S.A. European Patent Application No. EP 1 352 629. Cosmetic compositions containing prolyl hydroxylase inhibitors for stimulating hair growth.
3. Myllyharju J. Prolyl 4-hydroxylases, key enzymes in the synthesis of collagens and regulation of the response to hypoxia, and their roles as treatment targets. *Ann Med*. 2008;40(6):402-417.
4. Flagg SC, Martin CB, Taabazuing CY, Holmes BE, Knapp MJ. Screening chelating inhibitors of HIF-prolyl hydroxylase domain 2 (PHD2) and factor inhibiting HIF (FIH). *J Inorg Biochem*. 2012;113:25-30.
5. Santa Cruz Biotechnology. Product datasheet: 2,4-Diethylpyridine dicarboxylate, CAS 41438-38-4. Catalog No. sc-252391.
6. Kaelin WG Jr, Ratcliffe PJ. Oxygen sensing by metazoans: the central role of the HIF hydroxylase pathway. *Mol Cell*. 2008;30(4):373-383.
7. Ashimori A, Ono T, Uchida T, et al. Synthetic studies on pyridinedicarboxylic acid esters. *Chem Pharm Bull*. 1990;38(9):2446-2458.
8. MedChemExpress. Product datasheet: Diethyl pyridine-2,4-dicarboxylate. Catalog No. HY-100937.
9. Bernard BA. Advances in understanding hair growth. *F1000Res*. 2016;5:F1000 Faculty Rev-147. (Citing L'Oreal stemoxydine clinical data presented at EHRS 2012 and WCHR 2014.)
10. Juchaux F, Sellathurai T, Perrault V, et al. A combination of pyridine-2,4-dicarboxylic acid diethyl ester and resveratrol stabilizes hypoxia-inducible factor 1- $\alpha$  and improves hair density in female volunteers. *Int J Cosmet Sci*. 2020;42(2):167-173.

11. Mohyeldin A, Garzon-Muvdi T, Quinones-Hinojosa A. Oxygen in stem cell biology: a critical component of the stem cell niche. *Cell Stem Cell*. 2010;7(2):150-161.
12. Elattar Y. Trichoscopic evaluation of the effectiveness of topical stemoxydine for hair restoration in androgenetic alopecia: a prospective pre-post single-arm exploratory study. *J Cosmet Dermatol*. 2026;25:e70768.
13. Simon MC, Keith B. The role of oxygen availability in embryonic development and stem cell function. *Nat Rev Mol Cell Biol*. 2008;9(4):285-296.
14. Rebora A, Guarrera M. Kenogen: a new phase of the hair cycle? *Dermatology*. 2002;205(2):108-110.
15. L'Oreal S.A. Patent WO2016102489A1. Particular pyridinedicarboxylic acid derivative/antioxidant combination. Filed December 2015.
16. L'Oreal S.A. Patent EP 2 565 176. Cosmetic compositions comprising stemoxydine and resveratrol for hair density.
17. Semenza GL. Targeting HIF-1 for cancer therapy. *Nat Rev Cancer*. 2003;3(10):721-732.
18. Schofield CJ, Ratcliffe PJ. Oxygen sensing by HIF hydroxylases. *Nat Rev Mol Cell Biol*. 2004;5(5):343-354.
19. Vasta JD, Raines RT. Collagen prolyl 4-hydroxylase as a therapeutic target. *J Med Chem*. 2018;61(23):10403-10411.
20. Guarrera M, Rebora A. Kenogen in female androgenetic alopecia: a longitudinal study. *Dermatology*. 2005;210(1):18-20.
21. Yano K, Brown LF, Detmar M. Control of hair growth and follicle size by VEGF-mediated angiogenesis. *J Clin Invest*. 2001;107(4):409-417.
22. Kim JH, Lee SY, Myung SC. HIF-1 $\alpha$  stimulators function equally to leading hair loss agents in enhancing dermal papilla growth. *Arch Dermatol Res*. 2021;313(3):183-191.
23. L'Oreal Professionnel. Serioxyl Advanced Denser Hair clinical study summary. Product documentation, 2020.
24. Messenger AG, Rundegren J. Minoxidil: mechanisms of action on hair growth. *Br J Dermatol*. 2004;150(2):186-194.

25. Lachgar S, Charveron M, Gall Y, Bonafe JL. Minoxidil upregulates the expression of vascular endothelial growth factor in human hair dermal papilla cells. *Br J Dermatol*. 1998;138(3):407-411.
26. Vickers AE, Fischer V. Diaminopyrimidine oxide as a lysyl hydroxylase inhibitor: mechanism of anti-hair-loss activity. *J Cosmet Sci*. 2002;53(4):213-222.
27. Chen N, Hao C, Peng X, et al. Roxadustat for anemia in patients with kidney disease not receiving dialysis. *N Engl J Med*. 2019;381(11):1001-1010.
28. Olsen EA, Dunlap FE, Funicella T, et al. A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. *J Am Acad Dermatol*. 2002;47(3):377-385.
29. Kaufman KD, Olsen EA, Whiting D, et al. Finasteride in the treatment of men with androgenetic alopecia. *J Am Acad Dermatol*. 1998;39(4 Pt 1):578-589.
30. Rossi A, Cantisani C, Melis L, et al. Minoxidil use in dermatology, side effects and recent patents. *Recent Pat Inflamm Allergy Drug Discov*. 2012;6(2):130-136.
31. Irwig MS. Persistent sexual side effects of finasteride: could they be permanent? *J Sex Med*. 2012;9(11):2927-2932.
32. Induchem AG (Givaudan). Redensyl: targeting hair follicle stem cells for hair growth. Technical bulletin and clinical study data, 2014.
33. L'Oreal S.A. Kopexil technical documentation. Hair anchoring and anti-hair-loss activity. Internal product development data.

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