Leuphasyl

A Clinical Learning Guide for Medical Providers

Pentapeptide-18 (Tyr-D-Ala-Gly-Phe-Leu) • Enkephalin-Mimetic "Botox-Mimetic" • Skin Resilience

Evidence base at a glance: The second peptide in the Skin Resilience group — and a fundamentally different strategy from GHK-Cu (guide 1). Where GHK-Cu rebuilds the dermal matrix, Leuphasyl relaxes the muscles that crease it: it is a topical "Botox-mimetic" enkephalin analogue (Pentapeptide-18) that calms expression lines. Three facts dominate: (1) its mechanism is neuromuscular and UPSTREAM — a Leu-enkephalin mimic that binds the delta-opioid receptor, closes Ca^{2+} channels, and MODULATES (not blocks) acetylcholine release, softening muscle contraction; (2) it is purely COSMETIC and TOPICAL — no systemic use, no FDA drug pathway, with its signature value being SYNERGY with Argireline (the "Argirelox" combination); and (3) the evidence is thin and conflicted — reported ~28–35% wrinkle reduction at 2%, but ALL data are manufacturer-sponsored, open-label, with ZERO RCTs, no human PK, and genuine doubt about whether topical peptide reaches dermal nerve terminals at all. NOT FDA-approved (cosmetic ingredient).

1. Peptide Profile

Name: Leuphasyl (INCI: Pentapeptide-18); manufactured by Lipotec/Lubrizol

Classification: Topical neurotransmitter-inhibitor peptide; synthetic enkephalin-mimetic ("Botox-mimetic" cosmetic active)

Structure: Pentapeptide — 5 amino acids (Tyr-D-Ala-Gly-Phe-Leu); ~569.6 Da; a stabilized mimic of Leu-enkephalin (the D-Ala substitution resists enzymatic breakdown)

Mechanism class: Enkephalin/delta-opioid receptor agonist → Ca^{2+}-channel closure → reduced acetylcholine (ACh) release at the neuromuscular junction

Primary use: Topical anti-wrinkle (expression lines): forehead (frontalis), frown (corrugator), crow's feet (orbicularis oculi)

Routes: Topical only — serum/cream (2–10% solution; ~0.05% peptide per 5% solution). No systemic, SC, or injectable use

Regulatory status: NOT an FDA-approved drug; regulated as a cosmetic ingredient. Legal cosmetically provided no mechanistic/drug claims are made

Where It Sits in the Skin Resilience Group

This is the second peptide in the Skin Resilience category, and it represents the OTHER major topical strategy. GHK-Cu (guide 1) works on the dermal matrix — building collagen and elastin from the structural side. Leuphasyl works on the neuromuscular side — reducing the repeated muscle contractions that fold the skin into expression lines in the first place. The two are complementary rather than competing: one improves the canvas, the other reduces the creasing. Leuphasyl belongs to the "muscle-relaxing" cosmetic-peptide family alongside Argireline and SNAP-8, all of which approximate the effect of botulinum toxin (BoNT-A) without injection.

A Topical Cosmetic, Not a Therapeutic Peptide

Unlike most peptides in this collection, Leuphasyl has no systemic or injectable identity at all. It is a cosmetic ingredient whose entire evidence base is topical and manufacturer-generated. This shapes everything that follows: the relevant question is not "what dose, what route, what systemic effect," but "does a topically applied peptide actually reach motor nerve terminals deep enough to matter, and is the cosmetic benefit real and independently verified?" — questions the current evidence cannot fully answer.

2. Modes of Action & Mechanisms

Leuphasyl mimics Leu-enkephalin, the body's own opioid neuropeptide. By engaging the delta-opioid receptor on presynaptic motor-nerve terminals, it dampens the calcium signal that triggers acetylcholine release — reducing the intensity of muscle contraction and, over weeks, softening expression wrinkles. Crucially, it acts UPSTREAM of where Argireline and Botox act.

The Enkephalin / Delta-Opioid Cascade (step by step)

- **Receptor binding:** Leuphasyl binds delta-opioid (enkephalin) receptors on the presynaptic membrane — receptors coupled to inhibitory Gi proteins
- **G-protein dissociation:** the Gi protein splits into α, β, γ subunits that act on ion channels
- **Ca^{2+} channels close, K^{+} channels open:** calcium entry is blocked and potassium efflux holds the neuron at a negative resting potential — keeping it "quiet"
- **Vesicle fusion prevented:** without the Ca^{2+} influx, ACh-containing vesicles can't fuse with the membrane
- **ACh MODULATED, not blocked:** less acetylcholine reaches the synaptic cleft — contraction intensity falls but is not abolished; the effect is fully reversible
- **Progressive smoothing:** repeated application over weeks attenuates expression lines

Upstream vs Downstream: Leuphasyl vs Argireline vs Botox

The neuromuscular-peptide family is best understood as different points of attack on the same ACh-release cascade. This is also why combinations are synergistic — hitting two different steps does more than doubling either alone.

Agent	Target	ACh Release	Reversibility
Leuphasyl (Pentapeptide-18)	Enkephalin/delta-opioid receptor (Gi) — UPSTREAM (Ca^{2+} entry)	Modulated (reduced)	Fully reversible
Argireline (Acetyl Hexapeptide-8)	SNARE complex / SNAP-25 (midstream)	Reduced	Fully reversible
BoNT-A (Botox)	Enzymatic cleavage of SNAP-25	Blocked	Months

In Vitro Proof: Neurotransmitter (Glutamate) Release

Mechanism was demonstrated in neuronal cultures using glutamate release as a proxy for ACh release. Leuphasyl 1 mM inhibited release ~32% (vs Argireline ~20% and BoNT-A 50 nM ~57%). The key finding: Leuphasyl 1 mM + Argireline 1 mM together reached ~57% inhibition —

matching BoNT-A and exceeding the simple sum — confirming that the two peptides act by independent, synergistic mechanisms.

Emerging Property: Anti-Melanogenic (D-Tyrosine Analog)

A distinct research direction (Park 2020): adding D-tyrosine (a known tyrosinase inhibitor) to the peptide's C-terminus reduced melanin content in human melanocytes and inhibited tyrosinase more effectively than D-tyrosine alone, and slowed UV-/α-MSH-induced pigmentation in a skin model — raising the prospect of a dual anti-wrinkle + skin-brightening cosmeceutical. This is in vitro only; there are no clinical anti-pigmentation data.

Mechanistic takeaway: Leuphasyl is a reversible, topical "muscle-relaxer" that works UPSTREAM — quieting the calcium trigger for acetylcholine release via the enkephalin/delta-opioid pathway. Because it hits a different step than Argireline (SNARE) or Botox (SNAP-25 cleavage), it is genuinely synergistic in combination. The mechanism is well-described in vitro; whether it operates meaningfully after topical application in human skin is the open question.

3. Points of Clinical Relevance

1. It is a topical cosmetic, not a Botox replacement — set expectations

Leuphasyl softens expression lines modestly and reversibly; it does not match injectable botulinum toxin in degree or duration. The reported ~28–35% wrinkle reduction (2%, 60 days) is meaningful for a topical but is a gradual cosmetic effect, not a substitute for BoNT-A. Frame it as an adjunct or a needle-free option for those who decline injection.

2. Synergy with Argireline ("Argirelox") is its signature use

Because Leuphasyl acts upstream (Ca^{2+} channels) and Argireline midstream (SNARE/SNAP-25), the combination is additive-to-synergistic: combined ~24.6% mean wrinkle reduction vs ~16% (Argireline) and ~12% (Leuphasyl) alone. The two are routinely paired, and SNAP-8 is another synergistic partner. In practice, Leuphasyl is rarely used alone.

3. Concentration and application site are decisive

Only the 2% concentration produced significant improvement in the dose-finding study (0.5% and 1% did not), establishing ~2% as a practical threshold. Equally important, it must be applied across the whole mimic-muscle area (frontalis, corrugator, orbicularis oculi) — not just on the visible wrinkle — because the target is the muscle, not the line.

4. The central uncertainty: does topical peptide reach the nerve terminal?

The lecturer is candid that the biggest open question is whether a topically applied pentapeptide penetrates deeply enough to reach motor-nerve terminals at a concentration sufficient to modulate ACh — there are no dermatopharmacokinetic or skin-penetration studies, and peptide stability in cosmetic formulations is poorly characterized. It is genuinely unsettled how much of the clinical effect is the peptide versus the formulation vehicle.

5. It may extend or complement Botox — with appropriate caution

A manufacturer study reported that Argirelox cream nearly tripled the anti-wrinkle effect of BoNT-A over 6 months, suggesting topical peptides may prolong injection benefits between sessions or allow lower doses. This is a single, sponsored, unreplicated study (n=22); additive neuromuscular suppression is theoretically possible, so a physician combining the two should monitor for excessive muscle relaxation.

6. Reassuring safety — but only at topical cosmetic doses, short-term

Across in vitro and cosmetic testing, Leuphasyl showed no cytotoxicity (fibroblasts/keratinocytes), no genotoxicity (Ames negative), no ocular irritation, and excellent skin compatibility (patch-test MDIS = 0). However, there is no systemic-absorption data, no long-term (>60 day) safety evaluation, and no data in pregnancy/lactation — so safety conclusions apply only to short-term topical cosmetic use.

4. General Dosing & Delivery Options

All dosing is topical and derived from manufacturer data and open-label studies — there are no RCTs, no independent verification, and no human pharmacokinetics. Leuphasyl is a cosmetic ingredient, not a drug. For educational context only.

Topical Dosing (the only route)

Formulation	Concentration	Frequency / Duration
Serum	2–10% solution (≈0.05% peptide per 5% solution)	Twice daily; minimum 28–60 days
Cream	2% Leuphasyl (threshold for significant effect)	Twice daily; 60 days
Argirelox combination	5% Leuphasyl + 5% Argireline	Twice daily; 28 days (additive/synergistic)

Application Protocol (critical for effect)

- **Apply over the whole mimic muscle, not just the wrinkle:** frontalis (forehead), corrugator supercilii (frown), orbicularis oculi (crow's feet) — the target is the muscle
- **Technique:** apply to clean, slightly damp skin; press/pat (don't rub); allow 1–2 min absorption before layering
- **Be patient:** the effect is cumulative — progressive smoothing over weeks of twice-daily use, not an acute change
- **Threshold matters:** below ~2% the dose-finding data showed no significant benefit

Complementary Actives & Combinations

- **Argireline / SNAP-8:** validated synergistic neuromuscular partners (different cascade steps)
- **GHK-Cu / Matrixyl (matrix peptides):** a multi-pathway pairing the lecturer favors — muscle relaxation plus collagen building (the two Skin Resilience strategies combined)

– **Hyaluronic acid, niacinamide, vitamin C/E:** hydration, barrier, and antioxidant support — complementary, theoretical

5. Evidence Profile

Evidence tier distribution: solid IN VITRO mechanism (glutamate-release assays) and reassuring cosmetic safety testing, but the efficacy evidence is entirely manufacturer-sponsored OPEN-LABEL cosmetic studies — ZERO randomized, placebo-controlled, double-blind trials; no independent replication; no human pharmacokinetics or skin-penetration data.

In Vitro — Mechanism (confirmed)

– Glutamate-release assay: Leuphasyl 1 mM ~32% inhibition; Leuphasyl + Argireline (1 mM each) ~57% — matching BoNT-A 50 nM and confirming synergy via independent mechanisms

– Truth-protocol axes: neurotransmitter (ACh) modulation CONFIRMED in vitro; vascular/angiogenic, neurotrophin, immune, and metabolic/mitochondrial axes — NO data (not its mechanism)

Clinical — Anti-Wrinkle (open-label, manufacturer)

Study / Agent	Design	Wrinkle Reduction
Dragomirescu 2014 (2% Leuphasyl)	Open-label, 60 d, imaging	Frontal 34.7%; periorbital 28.4% (only 2% significant)
Leuphasyl alone (5% solution)	14 volunteers, 28 d	Mean 11.6% (max 23.6%)
Argireline alone (5% solution)	14 volunteers, 28 d	Mean 16.3% (max 31.8%)
Argirelox (5% each)	15 volunteers, 28 d	Mean 24.6% (max 46.5%) — additive

Safety — Cosmetic Testing

– No cytotoxicity (human fibroblasts/keratinocytes); Ames-negative (no genotoxicity); HET-CAM non-irritating; oral LD50 >2500 mg/kg (rats); patch-test MDIS = 0 (excellent compatibility)

BoNT-A Complement (single sponsored study)

– Argirelox cream nearly tripled BoNT-A anti-wrinkle effect over 6 months (n=22, open-label, manufacturer) — no adverse events, but unreplicated

Critical gaps: ZERO randomized, placebo-controlled, double-blind trials and no independent replication of manufacturer efficacy data; NO pharmacokinetic/skin-penetration studies (so the core question — does topical peptide reach nerve terminals? — is unanswered); no receptor-binding (Kd) data in cutaneous neurons; no dose-response beyond 0.5–2%; no

head-to-head vs Argireline/SYN-AKE/BoNT-A; no long-term safety (>12 months); and no data in diverse skin types (Fitzpatrick IV–VI) or male skin. Anti-melanogenic activity is in vitro only.

6. Clinical Considerations

Cautions & Contraindications

- **Pregnancy & lactation:** insufficient data — avoid as a precaution
- **Broken or inflamed skin:** avoid application
- **Patch test:** recommended before first use if reaction is a concern
- **Long-term/continuous use (>60 days):** not formally evaluated

Interactions

- **BoNT-A (Botox):** potential additive neuromuscular suppression — a benefit (prolonging/extending effect) but monitor for excessive muscle relaxation when combined
- **Other neuromuscular peptides (Argireline, SNAP-8):** intended synergy — used deliberately in combination
- No drug–drug interaction data (cosmetic, topical use only); no systemic absorption studies

Monitoring (cosmetic)

Parameter	Note	Rationale
Wrinkle response	Imaging at baseline, 28 d, 60 d	Primary cosmetic endpoint; effect is gradual
Local tolerability	Erythema, pruritus; patch test	Detect irritation/allergy (rare)
Muscle relaxation (if + BoNT-A)	Watch for excessive relaxation	Theoretical additive neuromuscular effect
Skin barrier (optional)	TEWL before/after	Formulation tolerability

Safety Profile

- Excellent short-term topical safety: no cytotoxicity, genotoxicity, ocular or skin irritation; no serious adverse effects in available literature
- Limits: no systemic-absorption data; long-term (>60 day) safety unevaluated; no pregnancy/lactation data; all reassurance is at topical cosmetic concentrations

Regulatory Status

Leuphasyl (Pentapeptide-18) is NOT an FDA-approved drug; it is regulated as a cosmetic ingredient. Cosmetic use is legal provided marketing stays within “beauty” claims and does not assert the mechanistic/disease effects described here — making such claims would reclassify it as an unapproved drug. There is no pharmaceutical regulatory pathway and no systemic use.

7. Final Note

As the second peptide in the Skin Resilience group, Leuphasyl rounds out the topical toolkit by attacking aging from the opposite direction to GHK-Cu. Where GHK-Cu rebuilds the dermal matrix, Leuphasyl reduces the muscular contractions that fold skin into expression lines — a needle-free, reversible "Botox-mimetic" that works upstream in the acetylcholine-release cascade via the enkephalin/delta-opioid pathway. Its mechanism is elegant and well-characterized in vitro, its safety at cosmetic concentrations is reassuring, and its synergy with Argireline (Argirelox) is its most practical and best-supported use.

The honest framing is that the efficacy evidence is modest and entirely manufacturer-generated. There are no randomized, placebo-controlled trials, no independent replication, and — most importantly — no pharmacokinetic or skin-penetration data to confirm that a topically applied peptide actually reaches motor-nerve terminals at a meaningful concentration. The reported 28–35% wrinkle reduction is encouraging for a topical, but how much reflects the peptide versus the formulation vehicle is genuinely unresolved, and the effect is gradual and far milder than injectable botulinum toxin.

For the clinician, Leuphasyl is best positioned as a low-risk topical adjunct: a reasonable needle-free option for patients who decline injection, a synergistic partner to Argireline, and a possible complement to BoNT-A between sessions (with monitoring). It should be presented as a cosmetic, not a therapeutic — used at ≥2%, applied across the whole mimic muscle, paired thoughtfully, and ideally combined with a matrix peptide like GHK-Cu to address both the canvas and the creasing. Set expectations modestly and source genuine, well-formulated product.

Bottom line: A topical, reversible "Botox-mimetic" cosmetic peptide (Pentapeptide-18) and the second entry in the Skin Resilience group — a Leu-enkephalin mimic that acts UPSTREAM, closing Ca^{2+} channels via the delta-opioid receptor to MODULATE acetylcholine release and soften expression lines (~28–35% wrinkle reduction at 2%, 60 d). Its signature use is synergy with Argireline (Argirelox); it complements GHK-Cu (matrix) by relaxing muscle. Mechanism confirmed in vitro, but efficacy data are manufacturer open-label only — ZERO RCTs, no human PK, and real doubt about skin penetration to nerve terminals. Excellent short-term topical safety. NOT FDA-approved (cosmetic ingredient); topical only.

Selected References

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For educational and research purposes only. Not medical advice. Leuphasyl (Pentapeptide-18) is NOT an FDA-approved drug; it is a cosmetic ingredient with no systemic or injectable use. Its anti-wrinkle efficacy data are entirely manufacturer-sponsored open-label studies — there are no randomized controlled trials, no independent replication, and no human pharmacokinetic or skin-penetration data confirming it reaches nerve terminals. Safety data apply only to short-term topical cosmetic use. Second peptide in the Skin Resilience series (complements GHK-Cu). Based on lecture materials by William Seeds, MD — SSRP Institute | Cellular Medicine Education.