Melanotan II

A Clinical Learning Guide for Medical Providers

Non-Selective Melanocortin Agonist (MC1/3/4/5R) • Skin Resilience (2 of 2 Melanotans)

Evidence base at a glance: The second of the two Melanotans and the broad, potent, UNAPPROVED counterpart to Melanotan I. Three facts dominate: (1) it is a NON-SELECTIVE melanocortin agonist — it activates MC1R (pigment), MC3R (energy), MC4R (appetite + sexual function), and MC5R (exocrine), and it CROSSES the blood–brain barrier (unlike MT-I) — which is exactly why it tans potently AND produces erections, appetite suppression, nausea, and flushing; (2) it is NOT FDA-approved anywhere, with no completed Phase 3 trials — an FDA warning letter (2007) and warnings from EU/Australia/Ireland — and the products people actually buy are unregulated, frequently mislabeled, and contaminated; and (3) the safety burden is the real story — nausea (>50%), spontaneous erections, mole/nevi darkening, transient BP rise, and melanoma case reports (no proven causal link, but a genuine concern). Where a specific effect is wanted, FDA-approved alternatives exist: Melanotan I for EPP photoprotection, PT-141 for sexual desire. Completes the Skin Resilience series.

1. Peptide Profile

Name: Melanotan II (MT-II)

Classification: Synthetic, NON-selective melanocortin receptor agonist; cyclic analogue of α-MSH

Structure: Cyclic heptapeptide — Ac-Nle-c[Asp-His-D-Phe-Arg-Trp-Lys]-NH_2; ~1024 Da. Structural modifications (Nle^4, $D\text{-}Phe^7$, lactam bridge, terminal capping) make it superpotent and degradation-resistant

Receptor profile: MC1R (pigment), MC3R (energy/immune), MC4R (appetite + sexual function + autonomic tone), MC5R (exocrine) — ~1000× selectivity over MC2R (ACTH) only

Pharmacokinetics: Half-life ~33–40 min IV (~1–2 h effective SC); SC bioavailability ~80–90%; Tmax ~1–2 h; CROSSES the blood–brain barrier

Routes: Subcutaneous injection (abdomen/thigh). No approved formulation

Regulatory status: NOT approved anywhere — FDA warning letter (2007); EMA, Australia (TGA), and Ireland (HPRA, 2023) warnings. No completed Phase 3 trials. Sold only as a research/grey-market peptide

Completing the Melanotan Pair — and the Skin Resilience Group

This is the second of the two Melanotans and the final peptide in the Skin Resilience category. It is best understood directly against Melanotan I (the previous guide). Both share the same MC1R pigmentation biology, but they diverge sharply: Melanotan I is LINEAR, MC1R-SELECTIVE, does not meaningfully cross the blood–brain barrier, and is FDA/EMA-APPROVED (Scenesse for EPP). Melanotan II is CYCLIC, NON-SELECTIVE across MC1/3/4/5R, DOES cross the blood–brain barrier, and is approved NOWHERE. The trade-off is the whole story: MT-II tans faster and more potently and adds central sexual/appetite effects,

but at the cost of a much broader side-effect profile and the absence of any regulatory oversight or quality control.

Why "Non-Selective" Explains Everything

MT-II's defining property — hitting four melanocortin receptors at once and reaching the brain — is simultaneously the source of its appeal and its problems. MC1R gives the tanning; MC4R (centrally) gives the erections and appetite suppression; MC3R/MC4R contribute autonomic/cardiovascular effects; MC5R touches exocrine glands. There is no way to get only the tan: the same molecule that darkens skin also drives nausea, spontaneous erections, flushing, and blood-pressure changes. This is the central concept of the guide.

2. Modes of Action & Mechanisms

MT-II activates the melanocortin receptor family broadly. The pigmentation pathway is identical to Melanotan I's (MC1R→cAMP→MITF→eumelanin), but because MT-II also engages MC3R, MC4R, and MC5R and crosses the blood–brain barrier, it produces a wide range of additional central and peripheral effects.

MC1R: The Pigmentation Cascade (shared with MT-I)

- **Binding → cAMP → PKA → CREB:** MT-II binds MC1R on melanocytes, raising cAMP and activating PKA, which phosphorylates CREB
- **MITF induction:** CREB drives MITF, the master melanocyte transcription factor
- **Eumelanin synthesis:** MITF upregulates tyrosinase, TRP1, and DCT (TRP2) → photoprotective brown/black eumelanin; DCT helps keep pigment as antioxidant eumelanin rather than pro-oxidant pheomelanin

MC4R (Central): The Source of the "Extra" Effects

Effect	Detail
Sexual function	MC4R activation initiates erectile response and enhances desire (the basis of the related approved drug PT-141)
Appetite suppression	Reduces food intake via MC4R in the arcuate nucleus; selectively cuts high-fat consumption (lost in MC4R-knockout)
Thermogenesis	Increases energy expenditure independent of reduced intake
Autonomic / cardiovascular	Modulates sympathetic output — may raise heart rate and blood pressure
Oxytocin / behavior	Induces central oxytocin release (animal data); MC4R agonism augments naltrexone against binge drinking

Other Receptors & Broader Biology

- **MC3R:** energy homeostasis and immune modulation; cardioprotective in animal reperfusion-injury models
- **MC5R:** exocrine/sebaceous gland function

- **Immune modulation (α-MSH/MCR):** ↓ TNF-α, IL-1, IL-6, IL-8, IFN-γ; ↑ IL-10; inhibits NF-κB; activates Tregs and improves Th1/Th17 balance
- **Neuroprotection (animal):** nerve-regeneration and cisplatin-neuropathy protection (bell-shaped dose response); MC1R activation restores BBB integrity and reduces neuroinflammation

The Melanoma Paradox

Mechanistically, in vitro work suggests MT-II can SUPPRESS melanoma (upregulating PTEN, inhibiting COX-2 and AKT/NF-κB; camptothecin–MT-II conjugates target melanoma cells). Yet real-world case reports associate MT-II use with melanoma DEVELOPMENT. The most likely explanation is not direct carcinogenesis but confounding: users get more UV exposure (believing they are protected), often skip sunscreen, and MC1R variants independently raise melanoma risk — which MT-II may compound. No causal link is proven, but the signal warrants serious caution.

Mechanistic takeaway: MT-II uses the same MC1R pigmentation pathway as Melanotan I but adds broad MC3/4/5R activation AND brain access — so it tans potently while also driving sexual, appetite, autonomic, and immune effects. That non-selectivity is inseparable from its side-effect profile; you cannot get the tan without the rest.

3. Points of Clinical Relevance

1. It is unapproved everywhere — and the real-world product is the bigger risk

Unlike Melanotan I (approved for EPP) or PT-141 (approved for HSDD), MT-II has NO approval anywhere and no completed Phase 3 trials. Critically, the products people actually obtain are internet/grey-market peptides with unknown purity, frequent mislabeling (MT-I vs MT-II), and documented contamination — prompting formal warnings in the US, EU, Australia, and Ireland. The sourcing hazard often exceeds the pharmacology hazard.

2. Non-selectivity means you cannot separate the tan from the side effects

Because MT-II activates MC1/3/4/5R and reaches the brain, the same dose that tans also causes nausea (>50%), spontaneous/prolonged erections, appetite suppression, flushing, and yawning. Patients seeking only cosmetic tanning should understand these are not avoidable "extras" — they are intrinsic to the molecule's mechanism.

3. Proven effects exist — but human evidence is small and uncontrolled

The human data are real but thin: pigmentation in a 3-subject Phase I pilot, and erectile response in ~80–85% of men across two small Wessells trials (n=10 and n=20). Metabolic, neuroprotective, and immune effects are largely animal/in vitro. There are no large or long-term human trials for any indication, so efficacy claims rest on small studies and mechanism.

4. Melanoma and nevi surveillance is non-negotiable

MT-II darkens existing moles and nevi, and case reports link it (often with sunbed use) to melanoma. Even though no causal link is proven and the in vitro data are paradoxically anti-tumor, mandatory baseline and periodic full-body skin exams with dermoscopy and nevus photography are essential, with biopsy of any changing lesion. Personal or family history of

melanoma/skin cancer is a contraindication, and concurrent sunbed use is strongly discouraged.

5. Specific dangerous interactions: PDE5 inhibitors, skin procedures, hypertension

Three cautions stand out. Do NOT combine with PDE5 inhibitors (sildenafil/tadalafil) — priapism risk (discontinue immediately if an erection lasts >4 hours). Avoid around skin procedures (laser, microneedling, chemical peels, tattoos) — the lecturer has clinically seen hypersensitivity reactions with marked hyperpigmentation; separate them completely. And use extreme caution in hypertension — MC4R-driven sympathetic output can transiently raise BP, so check BP in the first 2 hours after the initial dose.

6. If a specific effect is the goal, an approved alternative is usually better

Much of MT-II's appeal maps onto effects that approved drugs deliver more safely: Melanotan I (Scenesse) for photoprotection in EPP, and PT-141 (Vyleesi) for sexual desire (HSDD in women). Where one of those indications is the actual goal, the approved, quality-controlled option is generally preferable to an unregulated multi-receptor peptide; MT-II's niche is essentially "everything at once," which is rarely what a patient actually needs.

4. General Dosing & Delivery Options

No FDA-approved dosing exists for any indication; all protocols are research-derived or empirical and off-label. Tachyphylaxis develops with continuous dosing, so intermittent protocols are used. Titrate to the MINIMUM effective dose by pigment response. Unregulated product is a major hazard. For educational context only.

Empirical Dosing by Use (research/off-label)

Use	Loading	Maintenance
Tanning / photoprotection	~200 µg SC daily × ~7 days	~100 µg SC 2×/week
Metabolic / appetite	~50 µg SC daily, titrate up	Adjust to effect (tachyphylaxis-limited)
Sexual stimulation	Effect occurs at most doses	~500–1000 µg for targeted use (priapism risk)
Phase I research dose	0.01–0.03 mg/kg SC every other day	0.025 mg/kg recommended

Titration, Administration & Storage

- **Titrate by pigment:** start low (e.g. ~250 µg), increase ~250 µg every 5–7 days, adjusting to pigmentation response — minimum effective dose is the goal
- **First dose in-office:** consider observing BP in the first 2 hours and counseling on nausea/erection effects

- **Reconstitution:** 1–3 mL bacteriostatic water, swirl gently; U-100 insulin syringe (29–31 g); SC abdomen/thigh, rotate sites
- **Storage:** refrigerate 2–8°C after reconstitution, protect from light, use within ~7 days, do not freeze
- **Purity:** only 98%+ material with quality control — a real limitation given grey-market sourcing

5. Evidence Profile

Evidence tier distribution: predominantly PRECLINICAL (animal/in vitro) with only small, uncontrolled human trials (n=3–20) for pigmentation and erectile response — NO completed Phase 3 trials for any indication, and no long-term human safety data. This is far weaker than the approved Melanotan I or PT-141 evidence bases.

Human — Small Trials (the only human efficacy data)

Study	Design	Key Finding
Dorr 1996 (pigmentation)	Phase I pilot, 3 males, single-blind	2/3 showed increased pigmentation after 5 doses; side effects: nausea, yawning, erections
Wessells 1998 (ED)	Double-blind crossover, 10 men	8/10 erections; tip rigidity >80% for ~38 min (vs 3 min placebo)
Wessells 2000 (ED)	20 men (psychogenic + organic)	17/20 erections; 68% increased desire (vs 19% placebo)

Preclinical — Mechanistic Breadth (animal / in vitro)

- Metabolic (animal): central MT-II reduces food intake; intermittent dosing evokes fat/weight loss; thermogenesis up; tachyphylaxis with continuous dosing
- Neuroprotection (animal): enhanced sensory recovery after sciatic nerve crush; partial protection against cisplatin neuropathy (bell-shaped dose response)
- Immune (reviews/animal): ↓ TNF-α/IL-6/IFN-γ, ↑ IL-10, NF-κB inhibition, Treg activation
- Anti-cancer (in vitro): PTEN upregulation, COX-2/AKT/NF-κB inhibition; camptothecin–MT-II conjugate inhibits A375 melanoma (IC50 ~16 nM) — paradoxical vs the clinical melanoma case reports

Safety Signals (case reports & toxicology)

- Melanoma/dysplastic nevi: multiple case reports (e.g. melanoma after 3–4 weeks MT-II + sunbed; enlarging nevi in FAMMM) — no proven causal link, likely confounded
- Severe toxicity with massive overdoses from unregulated product: rhabdomyolysis and priapism reported

Critical gaps: NO completed Phase 3 trials for any indication; human efficacy rests on tiny studies (n=3–20); no long-term safety data; melanoma causality is unresolved (case reports, confounded by UV exposure and MC1R variants); and — uniquely important here — the

unregulated supply means purity, dose accuracy, and contamination are often unknown. The anti-tumor in vitro data and the melanoma case reports remain unreconciled.

6. Clinical Considerations

Contraindications

- **Personal or family history of melanoma or non-melanoma skin cancer:** contraindicated
- **PDE5 inhibitors (sildenafil/tadalafil):** do NOT combine — priapism risk
- **Pregnancy / lactation:** no safety data — contraindicated
- **Concurrent sunbed use:** strongly discouraged (melanoma case reports)
- **Skin procedures (laser, microneedling, peels, tattoos):** avoid — hypersensitivity/marked hyperpigmentation; separate completely

Cautions

- Hypertension / cardiovascular disease: MC4R-driven sympathetic output may transiently raise BP — monitor closely
- Men: counsel on spontaneous/prolonged erections; discontinue immediately if priapism (>4 h) develops
- Grey-market product: unknown purity/contamination is itself a contraindication to casual use

Adverse Events

Event	Frequency	Note
Nausea / vomiting	Very common (>50%)	Dose-related; often wanes over time
Spontaneous erection (males)	Very common	Can be prolonged; priapism risk with PDE5i
Facial flushing, yawning/stretching	Common	Mild, transient
Appetite suppression	Common	Mild–moderate
Mole / nevi darkening	Common	Dysplasia concern — surveillance required
BP elevation	Uncommon	Transient; caution in hypertension

Monitoring Protocol

Baseline: full skin examination with dermoscopy, photograph all nevi; BP; CMP/CBC. Ongoing: skin/nevi surveillance every 3–6 months (biopsy any changing lesion); BP each visit (and in the first 2 hours after the initial dose); CMP/CBC at baseline and ~every 3 months with continued use; query sexual side effects and inspect injection sites each visit. Titrate to the minimum effective dose by pigment response.

Comparison: MT-II vs MT-I vs PT-141

Feature	Melanotan II	Melanotan I	PT-141
Receptors	MC1/3/4/5R (non-selective)	MC1R-selective	MC3R/MC4R (selective)
BBB penetration	Yes	No	Yes
Pigmentation	Yes (potent)	Yes (primary)	Minimal (some in darker skin)
Sexual effects	Yes (MC4R, central)	No	Yes (primary indication)
FDA status	Not approved	Approved (EPP)	Approved (HSDD)

Regulatory Status

Melanotan II is NOT approved for human use anywhere — an FDA warning letter (2007) deems it illegal to market/sell in the US, with parallel warnings from the EMA, Australia's TGA, and Ireland's HPRA (2023). There are no completed Phase 3 trials. All use is off-label/investigational and requires documented informed consent covering melanoma concern, priapism, rhabdomyolysis, and the risks of unregulated product.

7. Final Note

As the second of the two Melanotans and the closing peptide of the Skin Resilience group, Melanotan II is best understood as Melanotan I's broad, potent, unregulated mirror image. It shares the same MC1R pigmentation engine, but its non-selective activation of MC3R, MC4R, and MC5R — plus its ability to cross the blood–brain barrier — turns it from a focused photoprotective agent into a whole-body melanocortin stimulant. That breadth is the source of both its appeal (rapid, potent tanning; erectile and appetite effects) and its liabilities (nausea, spontaneous erections, blood-pressure effects, and an inseparable side-effect profile).

The honest framing is that MT-II combines modest, small-trial human evidence with an outsized real-world risk. There are no Phase 3 trials, the human data amount to a handful of subjects, and the melanoma case reports — while not proving causation — are difficult to dismiss given that users tend to chase more sun with less protection, and that MC1R variants independently raise risk. Layered on top is the defining practical hazard of this peptide: the products people obtain are unregulated, frequently mislabeled, and contaminated, which is why regulators on three continents have issued warnings.

For the clinician, the most useful conclusion is comparative. Almost every individual effect patients seek from MT-II is delivered more safely by an approved, quality-controlled alternative — Melanotan I (Scenesse) for photoprotection, PT-141 (Vyleesi) for sexual desire. If MT-II is used at all, it demands genuine product, minimum effective dosing, intermittent protocols, strict skin and blood-pressure surveillance, avoidance of PDE5 inhibitors and skin procedures, and thorough informed consent. It completes the Skin Resilience picture by showing both the power of the melanocortin system and the cost of engaging it indiscriminately.

Bottom line: The NON-selective, potent, UNAPPROVED counterpart to Melanotan I and the final peptide in the Skin Resilience group — it activates MC1/3/4/5R and crosses the BBB, so it tans strongly while also driving erections, appetite suppression, nausea, flushing, and BP changes. Human evidence is small (pigmentation n=3; erectile response ~80–85% in n=10–20); most data are preclinical; melanoma case reports exist (no proven cause, likely confounded). Not approved anywhere (FDA/EMA/TGA/HPRA warnings); unregulated product is mislabeled/contaminated. Avoid PDE5i (priapism) and skin procedures (hyperpigmentation); mandatory skin/nevi and BP surveillance. Prefer approved alternatives — MT-I (EPP), PT-141 (HSDD) — where a specific effect is the goal.

Selected References

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For educational and research purposes only. Not medical advice. Melanotan II is NOT approved for human use anywhere (FDA warning letter 2007; EMA/TGA/HPRA warnings) and has no completed Phase 3 trials; all use is off-label/investigational. Human efficacy data are limited to small trials (pigmentation and erectile response); most evidence is preclinical. Melanoma case reports exist without proven causation. Unregulated "melanotan" products are not GMP-controlled and are frequently mislabeled (often confused with Melanotan I) and contaminated. Avoid PDE5 inhibitors (priapism) and skin procedures (hyperpigmentation); mandatory skin/nevi and blood-pressure surveillance. Where a specific effect is the goal, approved alternatives exist — Melanotan I (Scenesse, EPP) and PT-141 (Vyleesi, HSDD). Second of two Melanotan peptides, completing the Skin Resilience series. Based on lecture materials by William Seeds, MD — SSRP Institute | Cellular Medicine Education.