

RESEARCH MONOGRAPH . COMPOUND PROFILE

Topilitumide

A rationally designed, serum-labile topical antiandrogen engineered from the flutamide scaffold for androgen receptor suppression in dermal tissue without systemic absorption, developed by Biophysica Inc. and marketed as Eucapil for androgenetic alopecia in Central European jurisdictions.

DOCUMENT	KDC-MN-1519
ISSUED	2026-05-15
REVISION	1.0
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COMPOUND CLASS	Topical nonsteroidal antiandrogen of the perfluoroacylamido-arylpropanamide class with rapid serum hydrolysis and local androgen receptor suppression

ABSTRACT

Topilutamide (International Nonproprietary Name; also known as fluridil and by the development code BP-766) is a nonsteroidal antiandrogen of the perfluoroacylamido-arylpropanamide structural class, rationally designed for topical application in the treatment of androgenetic alopecia. The compound represents a deliberate medicinal chemistry solution to the principal limitation of systemic nonsteroidal antiandrogens such as flutamide, bicalutamide, and enzalutamide: hepatotoxicity and sexual adverse effects arising from systemic androgen receptor blockade. The design strategy incorporated perfluoroalkyl moieties into the flutamide analog BP-34 to produce a molecule that retains high-affinity androgen receptor antagonism and androgen receptor protein downregulation in dermal tissue while undergoing rapid hydrolytic decomposition upon contact with human serum (half-life approximately 6 hours at 37 degrees Celsius; undetectable after 48 hours), yielding the inactive fragments BP-34 and trifluoroacetic acid. Neither parent compound nor metabolites have been detected in human serum following chronic topical application at the marketed 2 percent concentration, establishing a pharmacokinetic profile that functionally eliminates systemic antiandrogenic exposure.

In vitro pharmacology in LNCaP human prostate cancer cells demonstrates concentration-dependent suppression of androgen receptor protein expression: approximately 40 percent reduction at 3 micromolar and up to 95 percent reduction at 10 micromolar following 48-hour incubation [1, 2]. Comparative binding studies suggest that topilutamide binds the androgen receptor with

approximately 9- to 15-fold greater affinity than bicalutamide and hydroxyflutamide, though these findings require further validation with rigorous competitive binding assays [2]. The mechanism appears to involve both direct receptor antagonism and receptor protein downregulation, distinguishing topilutamide from pure competitive antagonists that stabilize the receptor in an inactive conformation.

The clinical evidence base is limited to two published trials comprising 53 total participants. The pivotal randomized, double-blind, placebo-controlled trial in 43 men with androgenetic alopecia demonstrated significant promotion of anagen-phase hair growth: anagen percentage increased from 75.7 percent to 85.1 percent at 3 months and 87 percent at 9 months with daily topical application of 2 percent fluridil in isopropanol vehicle [3]. Sexual function, libido, hematology, and blood chemistry values remained within normal limits throughout the study period, and no systemic absorption of the parent compound or its metabolites was detectable. A second open-label study in 11 women with female pattern hair loss demonstrated significant increases in hair shaft diameter at 6 and 9 months but did not achieve statistical significance on anagen-telogen ratio endpoints [4]. The compound was introduced for cosmetic use in 2003 and is marketed exclusively in the Czech Republic and Slovakia by Interpharma Praha (a subsidiary of Otsuka Pharmaceutical) under the brand name Eucapil. It is not approved by the United States Food and Drug Administration, the European Medicines Agency, or any other major regulatory authority for pharmaceutical use. The patent expired in 2020. This monograph reviews the chemistry, synthesis, rational design strategy, androgen receptor pharmacology, pharmacokinetics and serum lability, preclinical toxicology, the clinical evidence base, sourcing and handling

considerations, comparator assessment against five alternative androgenetic alopecia agents, and the safety profile of topilutamide.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Topilutamide.

Common name: Fluridil. The common name is the predominant identifier in the clinical and consumer literature; the INN topilutamide is used in pharmacopoeial and regulatory contexts.

Development code: BP-766 (Biophysica Inc.). The development code derives from the parent compound BP-34 (the deacylated metabolite) and the series numbering within the Biophysica perfluoroacylamido-arylpropanamide program.

Marketed name: Eucapil (Interpharma Praha; Czech Republic, Slovakia).

Chemical Abstracts Service registry number: 260980-89-0.

Unique Ingredient Identifier (UNII): A8EU2FX13 (United States FDA Substance Registration System).

PubChem Compound Identifier: 9930988.

ChEMBL Identifier: ChEMBL2107790.

International Union of Pure and Applied Chemistry name: (2RS)-2-hydroxy-2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]-3-[(2,2,2-trifluoroacetyl)amino]propanamide. The IUPAC name reflects the racemic nature of the marketed material (one undefined stereocenter at the 2-position carbon bearing the hydroxyl and methyl substituents).

1.2 Structural class and chemistry

Topilutamide belongs to the perfluoroacylamido-arylpropanamide structural class, a small series of rationally designed molecules derived from the established nonsteroidal antiandrogen flutamide (2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]propanamide) by incorporation of a perfluoroacyl group (trifluoroacetyl) on the amino nitrogen of the propanamide side chain [1, 2]. The structural class is defined by the combination of an aryl ring bearing the nitro and

trifluoromethyl substituents characteristic of the flutamide pharmacophore with a perfluoroalkyl amide bond that confers hydrolytic lability in aqueous and serum environments.

Molecular formula: C₁₃H₁₁F₆N₃O₅.

Molecular weight: 403.237 g/mol.

Physical properties: White to off-white crystalline solid. Soluble in isopropanol, ethanol, dimethyl sulfoxide, and other organic solvents. Insoluble in water owing to the hydrophobic perfluoroalkyl moieties. The aqueous insolubility is a deliberate design feature that restricts the compound to lipophilic environments (dermal tissue, sebum, organic vehicles) and promotes hydrolytic decomposition upon contact with aqueous biological fluids.

Stereochemistry: Topilutamide contains one stereocenter at the 2-position carbon bearing the hydroxyl and methyl substituents. The marketed material is racemic (defined stereocenters: 0 of 1 per NCATS designation). Individual enantiomers have not been separately characterized for androgen receptor affinity or pharmacological activity in published literature; investigators conducting structure-activity relationship studies should consider enantiomeric resolution.

Hydrolytic lability: The trifluoroacetamide bond is the pharmacokinetically critical structural feature. Under physiological conditions (aqueous environment, 37 degrees Celsius, serum enzymes present), this bond undergoes hydrolysis with a half-life of approximately 6 hours, yielding BP-34 (the parent arylpropanamide, itself an inactive fragment) and trifluoroacetic acid [1, 5]. The hydrolysis proceeds faster in the presence of serum esterases and is essentially complete within 48 hours. This engineered instability is the molecular basis for the absence of systemic antiandrogenic activity.

1.3 Synthesis

The synthesis of topilutamide proceeds from the flutamide analog BP-34 (2-amino-2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]propanamide) by perfluoroacylation of the free amino group. The published synthetic approach involves:

1. Preparation of BP-34 from commercially available 4-nitro-3-(trifluoromethyl)aniline through standard amide coupling with 2-amino-2-methylpropanoic acid (alpha-aminoisobutyric acid) derivatives, followed by

hydroxylation at the 2-position.

2. Perfluoroacylation of the primary amine of BP-34 with trifluoroacetic anhydride or trifluoroacetyl chloride under mild conditions (typically in dichloromethane or tetrahydrofuran at 0 degrees Celsius to room temperature, with a tertiary amine base such as triethylamine or diisopropylethylamine to scavenge the generated acid) [2].
3. Purification by recrystallization or column chromatography, with characterization by nuclear magnetic resonance spectroscopy (^1H and ^{19}F), mass spectrometry, and high-performance liquid chromatography purity determination.

The synthesis is straightforward and the compound is manufactured at scale for the Eucapil product by Interpharma Praha. Research-grade material is available from multiple suppliers at greater than 98 percent purity. The patent (expired 2020) covered the specific perfluoroacylamido-arylpropanamide class and its topical dermatological applications [6].

2. Abstract

Topilutamide (fluridil, BP-766) is a topical nonsteroidal antiandrogen rationally designed to achieve local androgen receptor suppression in dermal tissue without systemic antiandrogenic exposure. The compound represents a medicinal chemistry solution to the fundamental limitation of systemic antiandrogen therapy for androgenetic alopecia: the sexual, hepatic, and endocrine adverse effects that arise from whole-body androgen receptor blockade. By incorporating a hydrolytically labile trifluoroacetamide bond into the flutamide pharmacophore, the designers produced a molecule that penetrates the lipophilic environment of the scalp dermis and hair follicle sebaceous unit, suppresses androgen receptor protein expression locally, and decomposes into inactive fragments upon contact with the aqueous environment of blood and interstitial fluid [1, 2, 3].

The clinical rationale is androgenetic alopecia, the most common form of progressive hair loss affecting approximately 50 percent of men by age 50 and 30 to 40 percent of women by menopause. Androgenetic alopecia is driven by the binding of dihydrotestosterone to androgen receptors in the dermal papilla of susceptible hair follicles, triggering follicular miniaturization, shortened anagen phase, and progressive conversion of terminal hairs to vellus hairs. Existing approved therapies (oral finasteride, oral dutasteride, topical minoxidil) address either upstream androgen biosynthesis (5- α reductase inhibitors) or follicular vascularity (minoxidil), but do not directly block the androgen receptor at the follicular level without systemic exposure. Topilutamide fills this mechanistic gap by providing direct, local androgen receptor antagonism with a self-inactivating pharmacokinetic profile [3, 5].

The compound was developed by Biophysica Inc. in the late 1990s, advanced through Phase 1 safety testing in 2002, and introduced as a cosmetic product (Eucapil) in 2003 in the Czech Republic and Slovakia through Interpharma Praha. Despite the mechanistic elegance of the design and the favorable safety profile demonstrated in clinical studies, the compound has not achieved broad regulatory approval or widespread commercial adoption. The clinical evidence base remains limited to two published trials with 53 total participants, and no Phase 3 registration trials have been conducted [3, 4]. The compound occupies a niche position in

the androgenetic alopecia treatment landscape: well characterized pharmacologically, rationally designed, clinically safe in limited testing, but insufficiently validated by the standards of major regulatory authorities.

3. Discovery and Development History

3.1 Rational design origin

The development of topilutamide originated in the research program of Marcel Sovak and colleagues at Biophysica Inc. during the late 1990s. The design premise was straightforward: systemic nonsteroidal antiandrogens (flutamide, bicalutamide, nilutamide) are potent androgen receptor antagonists with demonstrated efficacy in androgen-dependent conditions, but their systemic administration produces unacceptable adverse effects for a cosmetic indication such as hair loss, including hepatotoxicity, gynecomastia, sexual dysfunction, and metabolic disturbance [1, 2]. A topical antiandrogen that retained the receptor pharmacology of the flutamide class but was incapable of surviving in the bloodstream would, in principle, provide local efficacy without systemic liability.

The medicinal chemistry strategy exploited a known principle of prodrug and soft-drug design: incorporation of a metabolically labile bond that is stable in the delivery environment (lipophilic scalp tissue) but rapidly cleaved in the systemic environment (aqueous serum). The specific solution was the replacement of the stable acetamido group in the flutamide scaffold with a perfluoroacetamido group (trifluoroacetamide bond), producing a compound with rapid hydrolytic decomposition in aqueous environments while retaining stability in the lipophilic milieu of the hair follicle and sebaceous gland [2, 5].

3.2 Preclinical characterization

The preclinical characterization of topilutamide comprised three principal components: in vitro androgen receptor pharmacology, serum stability assessment, and animal toxicology.

In vitro pharmacology was conducted in LNCaP human prostate cancer cells (an androgen-sensitive cell line expressing functional androgen receptors). Topilutamide at 3 micromolar reduced androgen receptor protein expression by approximately 40 percent; at 10 micromolar, reduction reached approximately 95 percent after 48-hour incubation, as measured by Western blot analysis [1, 2]. These

concentrations are achievable in dermal tissue following topical application of the 2 percent formulation but are not achievable systemically owing to the rapid serum hydrolysis.

Serum stability was assessed in human serum at 37 degrees Celsius. The compound followed first-order hydrolysis kinetics with approximately 54 percent remaining at 6 hours and complete degradation by 48 hours, corresponding to a serum half-life of approximately 6 hours [5]. The hydrolysis products (BP-34 and trifluoroacetic acid) were confirmed as pharmacologically inactive with respect to androgen receptor binding.

Animal toxicology in mice and rats demonstrated low acute toxicity: oral LD50 exceeded 2000 mg/kg in both species; maximum tolerated dose in mice was 270 to 300 mg/kg/day acutely and 450 mg/kg/day subacutely [5]. Dermal studies in rabbits (twice-daily 1 percent application for 10 days) showed no cutaneous absorption, no sensitization, no phototoxicity, and no irritation. No fluridil or BP-34 was detectable in rabbit serum [5].

3.3 Phase 1 safety testing

Phase 1 clinical safety testing was initiated in 2002 with occlusive patch tests on human forearms at concentrations of 2 percent, 4 percent, and 6 percent in isopropanol vehicle over 21 days. The 2 percent concentration produced no irritation or sensitization. The 4 percent concentration was tolerated. The 6 percent concentration produced mild erythema in some subjects. The 2 percent concentration was selected for clinical development [3].

3.4 Market introduction

Topilutamide was introduced as a cosmetic product (not a pharmaceutical) under the brand name Eucapil in 2003 in the Czech Republic, with subsequent market extension to Slovakia. The product is manufactured and distributed by Interpharma Praha, a subsidiary of Otsuka Pharmaceutical Co., Ltd. The formulation is a 2 percent solution in isopropanol, supplied in single-use ampoules of 2 milliliters for nightly application to the scalp [3, 6].

The compound was registered as a cosmetic product rather than a pharmaceutical, a regulatory pathway that avoids the requirement for Phase 3 registration trials but restricts marketing claims and geographic reach. The compound has not been

submitted for pharmaceutical registration to the European Medicines Agency, the United States Food and Drug Administration, or other major regulatory authorities. The patent expired in 2020, removing intellectual property protection and potentially enabling generic formulation, though no generic products have achieved wide distribution outside Central Europe as of the monograph revision date.

3.5 Current status

The compound remains commercially available as Eucapil in the Czech Republic and Slovakia. Research-grade material is available from international chemical suppliers. No additional clinical trials have been reported since the initial publications in 2002 and 2004. The compound has not been advanced to Phase 2 or Phase 3 pharmaceutical registration trials. The research and commercial development of topilutamide appears to have stalled following the initial clinical publications, likely attributable to the small scale of the developing organization (Biophysica Inc.), the cosmetic (rather than pharmaceutical) regulatory pathway, and the limited commercial market accessible without broader regulatory approvals.

4. Mechanism of Action

4.1 Androgen receptor pharmacology

The androgen receptor is a nuclear steroid hormone receptor of the ligand-activated transcription factor class. In the hair follicle dermal papilla, binding of dihydrotestosterone (the 5-alpha-reduced metabolite of testosterone, produced locally by type II 5-alpha reductase) to the androgen receptor triggers a transcriptional program that shortens the anagen (growth) phase of the hair cycle, induces follicular miniaturization, and promotes the transition from terminal to vellus hair morphology. This androgen-driven miniaturization is the molecular basis of androgenetic alopecia in genetically susceptible individuals [7, 8].

Topilutamide acts at the androgen receptor through at least two characterized mechanisms:

Receptor antagonism: The compound competes with dihydrotestosterone and testosterone for binding at the ligand-binding domain of the androgen receptor, preventing receptor activation and nuclear translocation. Comparative affinity data suggest 9- to 15-fold greater binding affinity than bicalutamide and hydroxyflutamide, though these estimates require confirmation with rigorous radioligand displacement assays [2].

Receptor protein downregulation: At micromolar concentrations achievable topically, topilutamide reduces total androgen receptor protein levels (40 percent at 3 micromolar; 95 percent at 10 micromolar in LNCaP cells after 48 hours) [1, 2]. This downregulation goes beyond simple competitive antagonism: it reduces the cellular capacity for androgen signaling rather than merely blocking individual ligand-receptor interactions. The mechanism of the protein-level downregulation has not been fully characterized but may involve proteasomal degradation of the ligand-bound or antagonist-bound receptor complex, analogous to mechanisms characterized for other antiandrogens such as enzalutamide and ARV-110.

4.2 Distinction from 5-alpha reductase inhibitors

The mechanism of topilutamide is fundamentally distinct from that of finasteride and dutasteride, the principal approved pharmacotherapies for androgenetic alopecia in men. Finasteride and dutasteride inhibit the 5-alpha reductase enzyme (type II and types I/II respectively), reducing the conversion of testosterone to dihydrotestosterone. This upstream intervention reduces the androgenic ligand concentration but does not block the receptor itself; residual dihydrotestosterone and testosterone can still activate the androgen receptor. Topilutamide operates downstream at the receptor level, blocking androgen signaling regardless of the circulating or local androgen concentration [7, 8, 9].

4.3 Distinction from minoxidil

Minoxidil acts through a mechanism unrelated to androgen signaling. As a potassium channel opener and vasodilator, minoxidil promotes hair growth through enhanced follicular blood supply, prolongation of anagen, and direct mitogenic effects on follicular keratinocytes. Minoxidil does not affect androgen receptor signaling and its efficacy is independent of the androgen status of the hair follicle [10]. Topilutamide and minoxidil therefore represent mechanistically orthogonal approaches that could, in principle, be combined for additive or synergistic benefit.

4.4 Local versus systemic activity

The critical pharmacological feature of topilutamide is the restriction of antiandrogenic activity to the site of topical application. In the lipophilic environment of the hair follicle (sebum, stratum corneum lipids, dermal adipose tissue), the trifluoroacetamide bond is stable and the compound retains receptor affinity. Upon absorption into the aqueous compartment (interstitial fluid, blood), hydrolysis proceeds with a half-life of approximately 6 hours, converting the active antiandrogen into inactive fragments before systemic concentrations sufficient for receptor occupancy in distant tissues (prostate, hypothalamus, liver) can be achieved [5]. This pharmacokinetic self-inactivation eliminates the systemic antiandrogenic adverse effects (sexual dysfunction, gynecomastia, hepatotoxicity) that limit the use of systemic antiandrogens for hair loss indications.

5. Pharmacokinetics and Routes of Administration

5.1 Route of administration

Topilutamide is administered exclusively by the topical route. The marketed formulation (Eucapil) is a 2 percent solution in isopropanol vehicle, applied as 2 milliliters to the affected scalp area once nightly. The isopropanol vehicle promotes dissolution of the hydrophobic compound and enhances dermal penetration. Application is followed by drying without rinsing; the compound deposits in the lipophilic stratum corneum and follicular epithelium.

5.2 Dermal absorption and distribution

Following topical application, topilutamide partitions into the lipophilic compartments of the scalp: the stratum corneum, the sebaceous gland lipid phase, and the follicular canal. Local tissue concentrations are not precisely characterized in published literature but are inferred from the *in vitro* efficacy data (3 to 10 micromolar effective range in LNCaP cells) and from the observed clinical effects on anagen promotion. The compound is restricted to the lipophilic microenvironment by its aqueous insolubility and by the rapid hydrolysis that occurs at the lipid-aqueous interface [5].

5.3 Serum pharmacokinetics

Systemic pharmacokinetics are defined by the absence of detectable parent compound or metabolites in blood. In the pivotal clinical trial, neither topilutamide nor its hydrolysis product BP-34 was detectable in human serum (detection limit 5 ng/mL) at baseline, 3 months, or 90 days of daily 2 percent topical application [3]. This finding has been replicated in animal dermal absorption studies (rabbit model, twice-daily 1 percent application for 10 days) [5].

The mechanism of this non-absorption profile is twofold: (1) the hydrophobic compound has minimal aqueous solubility and therefore minimal passive diffusion into dermal capillaries; and (2) any compound that does reach the aqueous com-

partment is rapidly hydrolyzed (serum half-life approximately 6 hours, complete degradation by 48 hours).

5.4 Metabolism and elimination

Hydrolysis of the trifluoroacetamide bond yields two metabolites:

BP-34 (2-amino-2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]propanamide): The parent arylpropanamide fragment. This compound has been confirmed as pharmacologically inactive with respect to androgen receptor binding at achievable concentrations. Its systemic fate following any trace absorption has not been characterized in detail but is presumed to involve hepatic glucuronidation and renal excretion.

Trifluoroacetic acid: A small, highly polar perfluorocarboxylic acid that is rapidly eliminated renally. At the trace quantities potentially generated from topical application (milligram quantities of parent compound, with most hydrolysis occurring locally in dermal tissue), systemic trifluoroacetic acid concentrations are negligible relative to environmental background exposure.

Neither metabolite was detectable in human serum in clinical studies [3, 5].

5.5 Special populations

No specific pharmacokinetic studies in pediatric, geriatric, hepatically impaired, or renally impaired populations have been published, consistent with the cosmetic (rather than pharmaceutical) development pathway. Given the absence of systemic absorption, pharmacokinetic variability attributable to hepatic or renal function is not anticipated to be clinically relevant.

6. Preclinical Pharmacology

6.1 In vitro androgen receptor studies

The principal in vitro pharmacology data derive from studies in LNCaP human prostate cancer cells, an androgen-sensitive cell line that expresses functional androgen receptors and is the standard assay system for characterizing antiandrogen potency.

Androgen receptor protein downregulation: Topilutamide at 3 micromolar achieved approximately 40 percent reduction in androgen receptor protein expression; at 10 micromolar, reduction reached approximately 95 percent after 48-hour incubation, as measured by Western blot analysis [1, 2]. The concentration-response relationship was monotonic, with no evidence of an inverted-U dose-response.

Comparative binding affinity: Published estimates indicate that topilutamide binds the androgen receptor with approximately 9- to 15-fold greater affinity than bicalutamide and hydroxyflutamide [2]. These estimates are derived from functional assay comparisons rather than rigorous equilibrium radioligand displacement assays, and the precise K_i or IC_{50} values for competitive displacement of a reference ligand (such as [3H]-methyltrienolone or [3H]-dihydrotestosterone) have not been published.

Serum stability in vitro: First-order hydrolysis kinetics in human serum at 37 degrees Celsius: approximately 54 percent remaining at 6 hours, undetectable at 48 hours. Half-life approximately 6 hours [5].

6.2 Animal toxicology

Acute toxicity: Oral LD₅₀ exceeds 2000 mg/kg in both rats and mice, placing the compound in the lowest acute toxicity category [5]. Maximum tolerated dose in mice was 270 to 300 mg/kg/day acutely and 450 mg/kg/day subacutely.

Dermal toxicology (rabbit): Twice-daily application of 1 percent topilutamide in isopropanol vehicle for 10 days produced no local irritation, no sensitization, no phototoxicity, and no systemic absorption (parent compound and BP-34 unde-

tectable in serum) [5].

Dermal irritation (human, Phase 1): Occlusive patch testing at 2 percent, 4 percent, and 6 percent concentrations over 21 days demonstrated no irritation at 2 percent, acceptable tolerance at 4 percent, and mild erythema at 6 percent in some subjects [3].

6.3 Limitations of preclinical data

The preclinical data set for topilutamide is limited relative to pharmaceutical-grade development standards:

- No published competitive radioligand binding assays with characterized K_i or IC_{50} values at the human androgen receptor.
- No published studies of receptor selectivity against other nuclear receptors (progesterone receptor, glucocorticoid receptor, mineralocorticoid receptor, estrogen receptor).
- No published studies in isolated human hair follicle organ culture (the compound's aqueous instability prevents standard follicle culture assays).
- No published genotoxicity, carcinogenicity, or reproductive toxicology studies.
- No published chronic (greater than 28-day) animal toxicology studies.

These gaps reflect the cosmetic (rather than pharmaceutical) development pathway pursued by the sponsor. Investigators considering topilutamide for research applications beyond the marketed cosmetic indication should be aware that the compound has not been subjected to the full preclinical safety evaluation required for pharmaceutical registration.

7. Clinical Evidence Base

7.1 Pivotal trial in male androgenetic alopecia

Citation: Sovak M, Seligson AL, Kuceroval R, Bienova M, Hajduch M, Bucek M. Fluridil, a rationally designed topical agent for androgenetic alopecia: first clinical experience. *Dermatol Surg.* 2002;28(8):678-685 [3].

Design: Randomized, double-blind, placebo-controlled trial with open-label extension.

Population: 43 men, ages 20 to 56, with clinically diagnosed androgenetic alopecia (Hamilton-Norwood classification not specified in published data).

Intervention: 2 milliliters of 2 percent fluridil in isopropanol vehicle applied nightly to the vertex scalp. Placebo was isopropanol vehicle alone.

Duration: 3-month double-blind phase followed by 6-month open-label extension (all subjects receiving active treatment).

Primary endpoint: Phototrichogram assessment of anagen (growing) versus telogen (resting) hair percentage at the vertex.

Results (double-blind phase, 3 months):

- Fluridil group: anagen percentage increased from 75.7 percent to 85.1 percent; telogen decreased from 25.4 percent to 14.6 percent. Statistically significant difference from baseline and from placebo.
- Placebo group: no significant change in anagen percentage.

Results (open-label extension, 9 months total):

- Anagen percentage reached 87 percent at 9 months (minor additional gain beyond 3 months, suggesting plateau effect).
- Former placebo subjects who crossed over to active treatment showed anagen increase from 76 percent to 85 percent after 6 months of active treatment.

Safety:

- Sexual function, libido, and serum testosterone remained within normal limits throughout.
- Hematology and blood chemistry values were unremarkable.
- Neither fluridil nor BP-34 was detectable in serum at any time point (detection limit 5 ng/mL).
- No local irritation was reported at the 2 percent concentration.

Limitations: Small sample size (43 subjects); single-site study; phototrichogram as primary endpoint (lacks the standardized target area hair count methodology used in finasteride and minoxidil registration trials); limited duration; no assessment of hair count, hair density, or global photographic improvement by blinded assessment.

7.2 Open-label study in female androgenetic alopecia

Citation: Sovak M, Seligson AL, Kucerova R, Bienova M, Hajduch M, Bucek M. Development of fluridil, a topical suppressor of the androgen receptor in androgenetic alopecia. *Drug Dev Res.* 2004;62(2):103-108 [4].

Design: Open-label, single-arm study.

Population: 11 women (9 completed), ages 22 to 45, with female pattern hair loss.

Intervention: 2 milliliters of 2 percent fluridil in isopropanol applied nightly.

Duration: 9 months.

Endpoints: Hair shaft diameter (phototrichogram measurement), anagen-telogen ratio, global scalp imaging, participant self-assessment.

Results:

- Hair shaft diameter increased significantly at 6 and 9 months ($p < 0.05$).
- Anagen-telogen ratio showed no statistically significant change (small sample, high variability).
- Subjective improvement was reported by 5 of 11 participants (45 percent).
- Two participants withdrew owing to scalp irritation attributed to the isopropanol vehicle.

Limitations: No control group; very small sample (11 enrolled, 9 completed); open-label design susceptible to expectation bias; subjective endpoints predominated; 18 percent dropout rate attributed to vehicle irritation.

7.3 Absence of Phase 2 and Phase 3 data

No Phase 2 dose-finding studies, no Phase 3 registration trials, and no head-to-head comparisons with approved therapies (finasteride, minoxidil, dutasteride) have been published for topilutamide. The clinical evidence base therefore remains at the Phase 1/pilot efficacy level: sufficient to establish proof-of-concept and safety but insufficient for regulatory registration or confident assessment of comparative efficacy. The gap between the pharmacological promise and the clinical evidence reflects the development pathway constraints of a small organization pursuing cosmetic rather than pharmaceutical registration.

8. Sourcing and Quality Verification

8.1 Pharmaceutical-grade source

The only marketed pharmaceutical-grade formulation is Eucapil (Interpharma Praha), supplied as 2 percent topilutamide in isopropanol in single-use glass ampoules of 2 milliliters. This product is available through pharmacies in the Czech Republic and Slovakia and through online pharmacies that ship internationally from these jurisdictions. Product authenticity is confirmed by Interpharma Praha packaging, lot numbering, and certificate of analysis.

8.2 Research-grade sources

Research-grade topilutamide is supplied by multiple chemical vendors at greater than 98 percent purity by HPLC:

- Selleck Chemicals (catalog S7161)
- MedChemExpress (catalog HY-10122)
- TargetMol (catalog T4132)
- Cayman Chemical
- Tocris Bioscience
- AdooQ Bioscience
- AbMole BioScience
- GlpBio

Supply is in milligram to gram quantities as the free base (the compound does not form a conventional salt owing to the absence of readily ionizable groups at physiological pH). Pricing is moderate, in the range of \$100 to \$400 per 100 milligrams of greater than 98 percent purity material at the time of monograph preparation.

8.3 Quality verification

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 (expected [M+H]⁺ of 404.07 by electrospray ionization)
- Nuclear magnetic resonance spectroscopy (19F NMR is particularly useful for confirming the presence and integrity of both the trifluoromethyl group and the trifluoroacetamido group)
- Assessment of hydrolytic integrity at the time of testing (the compound degrades in aqueous solutions; all analytical testing should be conducted in anhydrous organic solvent)
- Residual solvent analysis by gas chromatography

8.4 Storage considerations for sourcing

The compound's hydrolytic lability requires anhydrous storage conditions. Vendor material should be stored at minus 20 degrees Celsius under inert atmosphere (nitrogen or argon) with desiccant. Once opened, the compound should be used promptly or aliquoted under anhydrous conditions. Degradation in the solid state is slow at refrigerated or frozen temperatures, but exposure to moisture accelerates hydrolysis of the trifluoroacetamide bond.

9. Reconstitution and Handling

9.1 Solubility profile

Topilutamide is freely soluble in isopropanol (the marketed vehicle), ethanol, dimethyl sulfoxide, dimethylformamide, and acetone. It is sparingly soluble in acetonitrile and practically insoluble in water. The aqueous insolubility is intrinsic to the design; investigators requiring aqueous-phase experiments should note that the compound will undergo hydrolysis upon dissolution in aqueous buffer at physiological pH and temperature.

9.2 Stock solution preparation

For in vitro research applications, stock solutions are typically prepared at 10 to 50 millimolar in dimethyl sulfoxide. These solutions should be stored at minus 20 degrees Celsius in sealed, desiccated vials and used within 3 months of preparation. Repeated freeze-thaw cycles should be minimized; aliquoting for single-use is recommended.

For cell culture assays, dimethyl sulfoxide stock solutions are diluted into culture medium at the time of use. The final dimethyl sulfoxide concentration should not exceed 0.1 percent to avoid solvent toxicity to cultured cells. Investigators should note that dilution into aqueous culture medium initiates the hydrolytic degradation of topilutamide; the effective concentration of intact compound decreases over the incubation period (half-life approximately 6 hours at 37 degrees Celsius in serum-containing medium). Assay design should account for this progressive degradation.

9.3 Topical formulation

For topical research applications (animal models of androgenetic alopecia, dermal pharmacology studies), the compound is formulated at 1 to 5 percent in isopropanol or in propylene glycol-isopropanol-water vehicles. The marketed Eucapil

formulation (2 percent in isopropanol) represents the optimized vehicle for human scalp application. Application volumes of 1 to 2 milliliters cover the typical affected area of the vertex scalp.

9.4 Stability in formulation

In anhydrous isopropanol vehicle, topilutamide is stable for at least 24 months at room temperature (the shelf life of the marketed Eucapil product). In propylene glycol-containing vehicles, stability depends on the water activity of the formulation. Vehicles with water content greater than 5 percent may initiate hydrolysis over extended storage. Investigators formulating topilutamide for research applications should assess chemical stability by HPLC over the intended storage period.

9.5 Light and temperature sensitivity

The compound does not exhibit marked photosensitivity. Storage protected from direct light is reasonable practice but not critical. Temperature stability in the solid state is acceptable at refrigerated (2 to 8 degrees Celsius) and room temperature conditions for the anhydrous compound. Elevated temperatures (greater than 40 degrees Celsius) in the presence of moisture accelerate hydrolysis.

10. Stack Interactions and Combinations

10.1 Combination with 5-alpha reductase inhibitors

The combination of topilutamide (androgen receptor antagonist, topical) with finasteride or dutasteride (5-alpha reductase inhibitors, oral or topical) represents a mechanistically rational dual-blockade approach: reduction of the androgenic ligand (dihydrotestosterone) upstream combined with blockade of the receptor downstream. This combination has not been studied in clinical trials. In principle, additive or synergistic benefit on hair growth endpoints is plausible, with the topilutamide component providing local receptor blockade without contributing to the systemic 5-alpha reductase inhibitor adverse-event profile. Investigators considering this combination should monitor for any unexpected local adverse events (dermal irritation, follicular inflammation) but systemic pharmacokinetic interactions are not anticipated given the non-absorption profile of topilutamide.

10.2 Combination with minoxidil

The combination with topical minoxidil (2 percent or 5 percent solution) is mechanistically orthogonal: minoxidil provides vasodilatory and mitogenic stimulation while topilutamide provides androgen receptor blockade. No pharmacokinetic interaction is expected. Vehicle compatibility should be verified (both compounds are typically formulated in alcohol-based vehicles). Sequential application (minoxidil in the morning, topilutamide at night) avoids potential formulation incompatibilities and mirrors the labeled application schedules of both products.

10.3 Combination with other topical antiandrogens

Concurrent topical use with other antiandrogens (topical bicalutamide, topical spironolactone, topical cyproterone acetate) is pharmacologically redundant for the androgen receptor antagonist mechanism. However, compounds with different

mechanisms of receptor interaction (competitive antagonism versus receptor degradation versus transcriptional cofactor disruption) could produce additive effects. No published data support or refute these combinations.

10.4 Combination with ketoconazole shampoo

Ketoconazole has weak androgen receptor antagonist activity and 5-alpha reductase inhibitory activity in addition to its antifungal mechanism. Combination with topilutamide is common in practice among androgenetic alopecia patients using multi-agent regimens. No characterized interaction is expected; the ketoconazole rinse-off formulation provides minimal sustained antiandrogenic activity.

10.5 Systemic drug interactions

Given the absence of systemic absorption, topilutamide has no characterized systemic drug-drug interactions. The compound does not undergo hepatic metabolism (it is hydrolyzed locally before reaching the liver) and therefore has no interactions with cytochrome P450 enzymes, P-glycoprotein, or other drug-metabolizing systems. Concurrent systemic medications (including oral finasteride, oral dutasteride, oral spironolactone, or oral bicalutamide) are not expected to interact pharmacokinetically with topical topilutamide.

10.6 Potential incompatibilities

The isopropanol vehicle may interact with concurrent topical medications that require specific pH or vehicle conditions. Retinoids (tretinoin, adapalene, tazarotene), benzoyl peroxide, and acidic preparations should be applied at different times of day to avoid vehicle-mediated interactions or precipitation. Concurrent application of aqueous-based topical medications to the same area could theoretically initiate hydrolysis of topilutamide at the skin surface, reducing local efficacy.

11. Adverse Events and Safety Signal

11.1 Local adverse events

The topical safety profile of topilutamide at the marketed 2 percent concentration is favorable:

- No irritation in Phase 1 occlusive patch testing over 21 days [3].
- No contact sensitization in repeat-insult patch testing [5].
- No phototoxicity in animal or human testing [5].
- Scalp irritation reported in the women's study was attributed to the iso-propanol vehicle rather than the active compound (2 of 11 withdrawals) [4].
- No folliculitis, dermatitis, or other inflammatory skin reactions attributed to topilutamide in published studies.

At higher concentrations (6 percent), mild erythema was observed in Phase 1 testing, establishing the concentration ceiling for the current formulation approach [3].

11.2 Systemic adverse events

No systemic adverse events have been attributed to topilutamide in published studies:

- Sexual function and libido were unaffected in the male clinical trial (no change from baseline, no difference from placebo) [3].
- Serum testosterone remained within normal limits throughout all study periods [3].
- Hematology and blood chemistry values were unremarkable [3].
- No hepatic enzyme elevations were observed (notably, the parent class compound flutamide carries a black-box warning for hepatotoxicity).
- No gynecomastia or breast tenderness was reported.

The absence of systemic effects is consistent with the pharmacokinetic profile: no detectable parent compound or metabolites in serum following chronic topical application.

11.3 Long-term safety

No long-term safety data (greater than 9 months) have been published for topilutamide. The compound has been marketed as Eucapil for over 20 years in the Czech Republic and Slovakia without published pharmacovigilance signals, though the absence of published postmarketing surveillance data should not be interpreted as definitive evidence of long-term safety. The theoretical long-term concern would be chronic exposure to trifluoroacetic acid (a persistent environmental contaminant and fluorochemical metabolite) at the skin surface, though the quantities generated from topical application are trivial relative to environmental exposure.

11.4 Contraindications and precautions

No formal contraindications have been established through pharmaceutical regulatory review. Reasonable precautions based on mechanism and formulation include:

- Broken or inflamed skin at the application site (the isopropanol vehicle would produce stinging; any increased absorption through compromised barrier would be mitigated by serum hydrolysis but has not been formally tested).
- Known allergy or sensitivity to isopropanol or other formulation components.
- Pregnancy and lactation (no human data; the compound is unlikely to produce systemic exposure, but formal safety in pregnancy has not been established).

11.5 Comparison to systemic antiandrogen safety

The safety advantage of topilutamide relative to systemic antiandrogens is its defining pharmacological feature:

- Finasteride (oral): associated with sexual dysfunction (erectile dysfunction, decreased libido, ejaculatory disorder) in 2 to 8 percent of users; rare depression and persistent sexual adverse effects reported postmarketing.
- Dutasteride (oral): similar sexual adverse-event profile to finasteride; additional concern for prostate cancer risk signal in the REDUCE trial.
- Bicalutamide (oral): hepatotoxicity, gynecomastia, breast tenderness; used off-label for female androgenetic alopecia but carries significant systemic adverse-event burden.
- Spironolactone (oral): hyperkalemia, menstrual irregularity, breast tenderness, orthostatic hypotension; used off-label for female androgenetic alopecia.

Topilutamide, by design, avoids all of these systemic adverse effects through its non-absorptive pharmacokinetic profile.

12. Comparative Assessment

This section presents a structured comparative assessment of five alternative androgenetic alopecia agents against topilutamide, evaluated against five competency standards: novelty (mechanistic originality), effect size (clinical efficacy magnitude), promising potential (development trajectory and regulatory status), side-effect profile, and overall validation (quality and depth of evidence base). The five comparators were selected as the principal approved or investigational agents that address androgen-mediated hair loss through distinct mechanisms.

12.1 Finasteride (oral)

Mechanism: Competitive inhibitor of type II 5-alpha reductase; reduces scalp dihydrotestosterone by approximately 60 to 70 percent without direct androgen receptor antagonism [9].

Novelty: Low. The mechanism is well established (approved 1992 for benign prostatic hyperplasia; 1997 for androgenetic alopecia). No mechanistic novelty relative to topilutamide.

Effect size: Moderate to large. The pivotal Phase 3 trials (n = 1553) demonstrated increases in hair count of 11 to 12 percent over placebo at 12 months in the vertex region; 83 percent of finasteride-treated men maintained or increased hair count versus 28 percent on placebo at 2 years [9]. Global photographic improvement was rated by blinded investigators. The effect size substantially exceeds what topilutamide has demonstrated in its smaller trials.

Promising potential: Fully realized. Finasteride is the first-line oral pharmacotherapy for male androgenetic alopecia, approved in over 60 countries, and is the comparator standard for all subsequent hair loss drug development.

Side-effect profile: The principal liability. Sexual adverse events (decreased libido, erectile dysfunction, ejaculatory disorder) occur in 2 to 8 percent of users in registration trials; persistent sexual dysfunction after discontinuation has been reported in postmarketing surveillance. The "post-finasteride syndrome" (while debated in its mechanistic basis) represents a significant concern that limits uptake and compliance.

Overall validation: Very high. Phase 3 registration data in over 1500 subjects; 25 years of postmarketing experience; extensive real-world data.

Comparison to topilutamide: Finasteride has vastly greater clinical validation, larger demonstrated effect sizes, and established regulatory status. Topilutamide has the theoretical advantage of avoiding systemic antiandrogenic exposure (and thereby the sexual adverse-event signal), but this advantage has not been demonstrated in comparative trials. Topilutamide blocks the receptor directly (downstream) while finasteride blocks ligand production (upstream); the two mechanisms are complementary.

12.2 Dutasteride (oral)

Mechanism: Dual inhibitor of type I and type II 5-alpha reductase; reduces scalp dihydrotestosterone by approximately 90 percent, greater than finasteride [11].

Novelty: Low. Mechanistically incremental over finasteride (broader enzyme inhibition, same pathway).

Effect size: Moderate to large. Head-to-head comparison with finasteride at 24 weeks showed statistically significant superiority in hair count change (dutasteride 0.5 mg: +12.2 hairs/cm² versus finasteride 1 mg: +4.7 hairs/cm² from baseline in the vertex target area) [11]. Meta-analyses suggest similar overall efficacy to finasteride with possible slight superiority in some populations.

Promising potential: High. Approved for androgenetic alopecia in Japan and South Korea; used off-label extensively worldwide; increasingly recognized as a second-line option for finasteride non-responders.

Side-effect profile: Similar to finasteride with the same class of sexual adverse events. The REDUCE trial raised a prostate cancer signal (increased detection of high-grade tumors) that complicates the risk-benefit assessment for a cosmetic indication. Long half-life (3 to 5 weeks) produces prolonged adverse-effect duration after discontinuation.

Overall validation: High. Phase 3 registration data; long-term extension studies; established in multiple jurisdictions.

Comparison to topilutamide: Dutasteride shares finasteride's advantages (large evidence base, regulatory status) and disadvantages (systemic sexual adverse effects) relative to topilutamide. The non-absorption profile of topilutamide remains its distinguishing feature versus both 5-alpha reductase inhibitors.

12.3 Topical minoxidil

Mechanism: Potassium channel opener and vasodilator; promotes hair growth through enhanced follicular perfusion and direct mitogenic effects on follicular keratinocytes. Mechanism is independent of androgen signaling [10].

Novelty: Low. Approved for hair loss since 1988; mechanism well established.

Effect size: Moderate. The 5 percent topical formulation produces approximately 10 to 15 percent increase in non-vellus hair count at 12 months in the vertex area [10]. Response rates are approximately 30 to 40 percent for moderate improvement. Effect is maintenance-dependent (hair loss resumes upon discontinuation).

Promising potential: Fully realized. First-line topical therapy for both male and female androgenetic alopecia; approved in over 100 countries; available over the counter.

Side-effect profile: Favorable for systemic safety. Local adverse events include scalp irritation (especially the propylene glycol-containing formulations), hypertrichosis of facial areas from inadvertent spread, and initial telogen effluvium ("shedding phase"). Rare cardiovascular effects (hypotension, tachycardia) have been reported with excessive application or in rare patients with increased absorption.

Overall validation: Very high. Multiple Phase 3 trials; decades of real-world use; extensive comparative data.

Comparison to topilutamide: Minoxidil operates through an entirely different mechanism (vasodilatory/mitogenic versus antiandrogenic) and is therefore a complement rather than a competitor to topilutamide. Both are topical agents with favorable systemic safety profiles. Minoxidil has vastly greater clinical validation. The combination of minoxidil and topilutamide is mechanistically rational but has not been clinically evaluated.

12.4 Topical bicalutamide

Mechanism: Pure nonsteroidal antiandrogen; competitive antagonist of the androgen receptor without agonist activity. Applied topically, bicalutamide provides local androgen receptor blockade [12]. Unlike topilutamide, bicalutamide is metabolically stable and can be absorbed systemically if applied in sufficient quantity.

Novelty: Moderate. Topical reformulation of an established oral antiandrogen represents a delivery innovation. The mechanism at the receptor level is similar to topilutamide.

Effect size: Limited clinical data for topical application in hair loss. The primary evidence base for bicalutamide in hair loss derives from oral use (off-label, primarily in women). Topical formulations are currently under investigation but lack published pivotal trial results.

Promising potential: Moderate. Increasing off-label use for female androgenetic alopecia. Topical formulations are being explored by compounding pharmacies. No dedicated regulatory registration for hair loss indication.

Side-effect profile: Oral bicalutamide carries hepatotoxicity risk and produces gynecomastia. Topical application reduces but does not eliminate systemic exposure (unlike topilutamide, which is fully inactivated upon absorption). The residual systemic risk from topical bicalutamide is poorly characterized.

Overall validation: Low for topical hair loss application. High for oral prostate cancer application. The topical hair loss use is off-label and investigational.

Comparison to topilutamide: Both are topical antiandrogens targeting the same receptor. Topilutamide's advantage is the engineered serum lability that guarantees non-systemic activity. Bicalutamide's advantage is the larger body of receptor pharmacology data and the established (oral) clinical track record. Topilutamide is the purer realization of the "topical-only antiandrogen" concept.

12.5 Clascoterone (topical)

Mechanism: Steroidal antiandrogen and androgen receptor antagonist; applied topically as a 1 percent cream (Winlevi, approved for acne) and under investigation for androgenetic alopecia [13]. Acts as a competitive antagonist at the androgen receptor in the dermal papilla.

Novelty: Moderate. The first topical antiandrogen to achieve FDA approval for a dermatological indication (acne, 2020). Application to androgenetic alopecia represents an extension of the approved mechanism to a new indication.

Effect size: Phase 2 data for androgenetic alopecia have been reported (Cassiopea SpA); the compound demonstrated improvements in target area hair count in dose-ranging studies. Phase 3 registration trials for androgenetic alopecia have been conducted. Published Phase 2 results suggest modest improvements in hair count endpoints.

Promising potential: High. Closest regulatory-stage competitor to the topical antiandrogen concept that topilutamide pioneered. FDA approval for acne validates the topical antiandrogen safety concept. Androgenetic alopecia Phase 3 data are expected.

Side-effect profile: Topical application is well tolerated; local adverse events are similar to vehicle (mild application site reactions). Systemic absorption is minimal but detectable (unlike topilutamide, which is undetectable). The cortexolone backbone is rapidly metabolized hepatically if absorbed. No sexual adverse effects reported in clinical trials.

Overall validation: Moderate to high. FDA-approved for one topical indication; Phase 2/3 data in androgenetic alopecia; regulatory-grade safety characterization.

Comparison to topilutamide: Clascoterone represents the modern, well-funded realization of the topical antiandrogen concept that topilutamide pioneered in the early 2000s. Clascoterone has larger clinical trials, a regulatory track record (FDA approval for acne), and a clear development pathway toward androgenetic alopecia approval. Topilutamide has the advantage of absolute non-absorption (versus minimal but detectable absorption for clascoterone) and a 20-year history of cosmetic use without safety signals. Clascoterone is likely to overtake topilutamide commercially if approved for hair loss, but topilutamide retains its position as the compound with the most complete elimination of systemic exposure.

12.6 Comparator summary

The five comparators occupy distinct positions in the androgenetic alopecia treatment landscape. **Finasteride** and **dutasteride** are the established oral pharmacotherapies with large effect sizes and extensive validation but carry the systemic sexual adverse-event liability that topilutamide was designed to avoid. **Topical mi-**

noxidil operates through a non-androgenic mechanism and is complementary rather than competitive. **Topical bicalutamide** shares the receptor-level mechanism but lacks the engineered non-absorption safety feature. **Clascoterone** represents the closest mechanistic and strategic competitor, with a modern regulatory development pathway that may achieve broad approval for the topical antiandrogen concept.

Topilutamide occupies a historical and pharmacological niche: it was the first deliberately designed self-inactivating topical antiandrogen, and its absolute non-absorption profile remains unique among antiandrogen candidates. Its clinical validation, however, is the weakest in the panel (53 total subjects, no Phase 3 data, no head-to-head comparisons with approved therapies). The compound is best positioned as a research tool for proof-of-concept topical antiandrogen pharmacology and as a cosmetic option for patients seeking to avoid any systemic antiandrogenic exposure, while acknowledging that the clinical evidence base does not meet modern pharmaceutical registration standards.

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