CLINICAL MONOGRAPH · NEURO & COGNITIVE (UNDER FDA REVIEW)

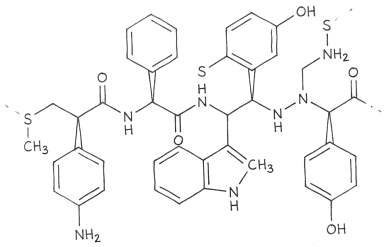
Vasoactive Intestinal Peptide (VIP)

Vasoactive intestinal peptide with case-by-case pharmacy review

Vasoactive intestinal peptide (VIP) is a small natural hormone, a chain of 28 amino acids, that the body makes in the nervous system, gut, lungs, and immune cells [bodanszky1974; prasse2010]. It relaxes blood vessels and airway smooth muscle, helps regulate inflammation, and influences gut, lung, and brain function. It was discovered in 1970 by Said and Mutt, who isolated it from pig intestine, and was first synthesized in the laboratory in 1974 [saidmutt1972; said2007].

Synthetic VIP and the closely related synthetic analogue aviptadil have been studied as drugs for several conditions. The most-discussed example is aviptadil for severe COVID-19 respiratory failure, the ZYESAMI program ran a randomized trial (TESICO) that did not meet its primary endpoint, and the drug was not approved [brown2023]. Inhaled VIP has been studied in small trials in pulmonary hypertension and sarcoidosis. In Europe a combination product (aviptadil plus phentolamine, brand name Invicorp) is authorized for erectile dysfunction by intracavernosal injection, but this product is not approved in the U.S [dinsmore2008]. Some integrative practitioners have used intranasal VIP in chronic inflammatory response syndrome (the Shoemaker protocol), but the published evidence for that use is weak [shoemaker2010].

VIP has no FDA approval in the United States. This ingredient is part of an evolving FDA review process. Physicians may submit patient-specific prescription requests for pharmacy review. Availability is determined case by case, and availability may change after FDA review, PCAC discussion, final agency action, or state-board guidance.



EVIDENCE POSTURE EMERGING PRECLINICAL REVIEWED **2026-05-11**

State-licensed 503A | Pharmacist reviewed | Doctor led | Cold-chain ready | Patient choice preserved

Contents

Click any section to jump there. Page numbers update on render.

FOR CLINICIANS

Vasoactive intestinal peptide (VIP) is an endogenous 28-amino-acid neuropeptide of the secretin/glucagon/PACAP superfamily, isolated from porcine intestinal wall by Said and Mutt and first chemically synthesized by Bodanszky and colleagues [saidmutt1972, bodanszky1974, said2007]. It signals through two class B G-protein-coupled receptors, VPAC1 and VPAC2, with downstream Gαs-mediated cAMP elevation and additional Gαq coupling; the closely related neuropeptide PACAP shares receptor pharmacology and is reviewed in the IUPHAR receptor nomenclature [harmar2012]. Physiologic actions include systemic and pulmonary vasodilation, bronchial and gastrointestinal smooth-muscle relaxation, exocrine and endocrine secretion modulation, neurotransmission in the suprachiasmatic nucleus and enteric nervous system, and broad anti-inflammatory and immunomodulatory effects on T cells, macrophages, and dendritic cells [iwasaki2019; vosko2015].

Clinical development as a synthetic drug, generally as VIP itself or as the synthetic analogue aviptadil, has been pursued across several indications with mostly negative or inconclusive late-stage results. Inhaled VIP/aviptadil produced acute pulmonary vasodilation and signals of clinical benefit in small open-label trials in pulmonary arterial hypertension [petkov2003, leuchte2008] but no large randomized confirmation has been reported and most U.S. development was discontinued. Inhaled VIP was studied in Phase 1 in pulmonary sarcoidosis with immunoregulatory and symptomatic signal [prasse2010] but did not advance to a confirmatory program. Intravenous and inhaled aviptadil were tested in COVID-19 critical respiratory failure: a single-center pre-print/Crit Care Med report described use in critically ill patients [youssef2022], and the multicenter randomized TESICO trial of IV aviptadil plus remdesivir vs remdesivir alone in hospitalized COVID-19 hypoxemic respiratory failure did not demonstrate benefit [brown2023]. A 2025 systematic review and meta-analysis of aviptadil in ARDS concluded the aggregate evidence does not support a survival or oxygenation benefit [udupa2025]. The intracavernosal combination of aviptadil with phentolamine (Invicorp) is approved in several European countries for erectile dysfunction [dinsmore2008, keijzers2001] but is not FDA-approved and intracavernosal compounding is not within RonanRx's scope. VIP-secreting tumors (VIPomas, Verner-Morrison syndrome) produce the WDHA syndrome and are a separate pathologic context informative for the peptide's physiology [belei2017] [henning2001; delgado2013].

VIP has no FDA approval in the United States. This ingredient is part of an evolving FDA review process. Physicians may submit patient-specific prescription requests for pharmacy review. Availability is determined case by case, and availability may change after FDA review, PCAC discussion, final agency action, or state-board guidance.

Why Personalized Vasoactive Intestinal Peptide (VIP)

The evidence base for VIP includes endogenous physiology, aviptadil clinical studies, and foreign-product context, but no FDA-approved US VIP or aviptadil product. Some US development programs did not meet approval standards, so patient-specific review must be cautious.

Physicians may submit patient-specific prescription requests for VIP for pharmacy review. Certain preparations may be available now when clinically appropriate, lawfully prescribed, supported by patient-specific documentation, and approved by the dispensing pharmacy. Availability is determined case by case. This is not a consumer access promise; it is a clinical, sourcing, formulation, and regulatory review process. This ingredient is part of an evolving FDA review process for peptide-related bulk substances used in compounding.

The legitimate path for VIP is not a protocol bought from an unregulated channel. It is a prescriber-submitted request reviewed by a licensed pharmacy against evidence, sourcing, sterile formulation, and patient-specific risk.

Quick Facts About Vasoactive Intestinal Peptide (VIP)

Category: Endogenous 28-amino-acid neuropeptide of the secretin/glucagon superfamily

Active ingredient: Vasoactive intestinal peptide (VIP), 28-amino-acid peptide isolated by Said and Mutt from porcine intestinal wall; synthetic VIP and the closely related synthetic analogue aviptadil are the forms studied clinically

FDA-approved branded forms: None in the United States. The combination intracavernosal product Invicorp (aviptadil + phentolamine) is approved in several European countries for erectile dysfunction but is not FDA-approved in the U.S. The aviptadil ARDS program (ZYESAMI/RLF-100) did not meet its primary endpoint and was not approved.

Evidence posture: Emerging clinical evidence in pulmonary hypertension, ARDS/COVID-19 respiratory failure, sarcoidosis, and intracavernosal erectile dysfunction; most U.S. clinical development discontinued. Preclinical literature broad and biologically plausible. No FDA-approved U.S. product.

FDA-approval status: Category 2, evolving FDA review process. Valid patient-specific prescription required; supporting clinical rationale may be requested.

Compounded under: Physicians may submit patient-specific prescription requests for pharmacy review. Availability is determined case by case.

SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY

Physicians may submit patient-specific prescription requests for Vasoactive Intestinal Peptide (VIP) for pharmacy review. Certain preparations may be available now when clinically appropriate, lawfully prescribed, and approved by the dispensing pharmacy. Availability is determined case by case.

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

How This Differs from a Research-Use-Only Website

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

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

What is Vasoactive Intestinal Peptide (VIP)?

Vasoactive intestinal peptide is a 28-amino-acid linear neuropeptide of the secretin/glucagon/PACAP family. The mature sequence (HSDAVFTDNYTRLRKQMAVKKYLNSILN-NH2) is produced from a larger precursor (prepro-VIP) that also yields the peptide histidine isoleucine (PHI, or its human homolog PHM) by tissue-specific post-translational processing. VIP is widely distributed across the central and peripheral nervous systems, enteric neurons, lung, pancreas, immune tissues, and reproductive tract, and acts as both a neurotransmitter and a paracrine/endocrine signal [saidmutt1972, said2007, iwasaki2019].

VIP was discovered by Sami Said and Viktor Mutt in 1970 during a search for endogenous vasodilators released from the lung and was named for its vasodilator activity isolated from intestinal extracts. The full 28-residue structure was reported by Said and Mutt in 1972 [saidmutt1972] and the first total chemical synthesis was completed by Bodanszky, Klausner, and Lin in 1974 [bodanszky1974]. The peptide's broad physiologic range, initially classified as a 'gut hormone,' later as a neurotransmitter, led Said to summarize the discovery history as a peptide 'initially looked for in the lung, isolated from intestine, and identified as a neuropeptide' [said2007].

VIP signals through two class B G-protein-coupled receptors, VPAC1 (VIPR1) and VPAC2 (VIPR2), which it shares with the closely related neuropeptide PACAP; PACAP additionally activates the PAC1 receptor selectively. The IUPHAR concise guide and Harmar review summarize the receptor pharmacology and tissue-expression patterns of the VIP/PACAP receptor family [harmar2012]. Synthetic VIP and the synthetic analogue aviptadil (the same 28-residue sequence supplied as a pharmaceutical-grade synthetic peptide) are the forms used in clinical research.

How Vasoactive Intestinal Peptide (VIP) Works

VIP exerts its effects through two related class B GPCRs, VPAC1 and VPAC2, both coupled primarily to Gαs with downstream adenylyl cyclase activation and intracellular cAMP elevation; secondary coupling to Gαq with phospholipase C and intracellular calcium mobilization has been characterized in several cell types [harmar2012]. The cAMP/PKA pathway underlies VIP's smooth-muscle relaxant and vasodilator effects in vascular, airway, and gastrointestinal smooth muscle [henning2001, groneberg2006].

In the immune system, VIP signaling shifts macrophage polarization toward an anti-inflammatory phenotype, inhibits Th1-skewing cytokines, supports regulatory T cell function, and suppresses NF-κB-driven proinflammatory cytokine transcription in dendritic cells and lymphocytes. Delgado and Ganea reviewed the pleiotropic immune functions of VIP as an endogenous anti-inflammatory neuropeptide and a candidate immunomodulatory drug class [delgado2013].

In the pulmonary circulation, VIP and aviptadil produce dose-dependent reduction in pulmonary vascular resistance with relatively selective pulmonary vasodilation when delivered by inhalation. In the airway, VIP relaxes bronchial smooth muscle and inhibits airway inflammation, a rationale for asthma and COPD drug development that has been reviewed extensively [onoue2007]. In the central nervous system, VIP is a key signaling peptide in the suprachiasmatic nucleus of the hypothalamus where it coordinates circadian rhythm entrainment and synchronization [vosko2015] [mathioudakis2013]. In the gastrointestinal tract, VIP relaxes intestinal smooth muscle and regulates fluid and electrolyte secretion; pathologic over-secretion by VIP-producing neuroendocrine tumors produces the WDHA (watery diarrhea, hypokalemia, achlorhydria) syndrome characteristic of VIPoma [belei2017, iwasaki2019] [groneberg2001].

Biological Role of Vasoactive Intestinal Peptide (VIP)

VIP is one of the most broadly distributed neuropeptides in mammalian physiology. It is co-stored and co-released with classical neurotransmitters from autonomic and enteric neurons, is expressed in CNS regions including the suprachiasmatic nucleus and cerebral cortex, and is produced by immune cells including T lymphocytes and macrophages. Physiologic roles include systemic and pulmonary vasodilation, airway and gut smooth-muscle relaxation, exocrine secretion (pancreatic, biliary, intestinal), endocrine modulation

(prolactin release, insulin secretion), central nervous system functions including circadian rhythm coordination in the SCN, and immune modulation [henning2001; delgado2013; vosko2015].

The receptor system is shared with the closely related neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP): both peptides activate VPAC1 and VPAC2 with comparable affinity, while PACAP additionally activates the selective PAC1 receptor [harmar2012] [iwasaki2019]. This receptor sharing complicates the interpretation of physiologic roles assigned to VIP versus PACAP and is one reason that VIP-knockout mice display compensatory phenotypes.

Vasoactive Intestinal Peptide (VIP) Research History

The story begins with Sami Said's search in the late 1960s for a vasodilator substance released from the lung. Collaborating with Viktor Mutt at the Karolinska Institute, who had isolated several gut peptides from porcine intestine, Said and Mutt extracted a vasodilator polypeptide from porcine duodenal wall and reported the 28-residue sequence in 1970 (Science) and in expanded form in 1972 (Eur J Biochem) [saidmutt1972]. Bodanszky, Klausner, and Lin completed the first total chemical synthesis of VIP in 1974 [bodanszky1974]. Said's 2007 retrospective summarized the discovery and the evolution of VIP's classification from gut hormone to neuropeptide [said2007].

The 1980s and 1990s established VIP's broad signaling roles. Henning and Sawmiller (2001) reviewed cardiovascular effects, including systemic and pulmonary vasodilation, coronary vasodilation, and inotropic and chronotropic effects [henning2001]. Groneberg and colleagues (2001, 2006) reviewed the pulmonary biology and the asthma/COPD drug-development rationale [groneberg2001, groneberg2006]; Onoue and colleagues (2007) summarized bioactive analogues and inhaled drug-delivery work [onoue2007]. Delgado and Ganea (2013) consolidated the immunomodulatory literature [delgado2013]. The Harmar IUPHAR review (2012) systematized the VPAC1/VPAC2/PAC1 receptor pharmacology shared with PACAP [harmar2012]. Iwasaki and colleagues (2019) reviewed recent advances in VIP physiology and pathophysiology with a focus on the gastrointestinal system [iwasaki2019]. Vosko and colleagues (2015) reviewed the role of VIP in the suprachiasmatic light-input circadian system [vosko2015].

Clinical drug development. The synthetic peptide (named aviptadil when supplied as a pharmaceutical-grade product) has been studied in: (1) primary/pulmonary arterial hypertension, Petkov and colleagues (2003) reported acute hemodynamic and chronic clinical improvement with inhaled aviptadil in a small uncontrolled trial in J Clin Invest [petkov2003]; Leuchte and colleagues (2008) reported single-dose hemodynamic effects in pulmonary hypertension [leuchte2008]; (2) pulmonary sarcoidosis, Prasse and colleagues (2010) reported immunoregulatory effects of inhaled VIP in a Phase 1 study [prasse2010]; (3) erectile dysfunction, intracavernosal aviptadil/phentolamine (brand Invicorp) was developed and is approved in several European countries [dinsmore2008, keijzers2001]; (4) acute respiratory distress syndrome and COVID-19, Youssef and colleagues (2022) reported on IV aviptadil in critically ill COVID-19 patients [youssef2022], and the U.S. ACTIV-3b/TESICO multicenter trial of IV aviptadil plus remdesivir vs

remdesivir in COVID-19 hypoxemic respiratory failure (Brown and colleagues, Lancet Respir Med 2023) reported no benefit [brown2023]; Udupa and colleagues (2025) performed a systematic review and meta-analysis of aviptadil in ARDS and concluded the evidence does not support survival or oxygenation benefit [udupa2025]. Mathioudakis and colleagues (2013) reviewed the inhaled-VIP literature across respiratory indications [mathioudakis2013]. Most U.S. clinical development for inhaled or IV VIP/aviptadil has been discontinued.

Vasoactive Intestinal Peptide (VIP) Timeline

1970 • Said and Mutt report isolation of a vasodilator polypeptide from porcine duodenal extracts in Science [said2007]

1972 • Said and Mutt publish the full 28-residue VIP sequence in Eur J Biochem [saidmutt1972]

1974 • Bodanszky, Klausner, and Lin (J Am Chem Soc) complete the first total chemical synthesis of VIP [bodanszky1974]

2001 • Henning and Sawmiller (Cardiovasc Res) review the cardiovascular effects of VIP, summarizing pulmonary and systemic vasodilation and inotropic and chronotropic effects [henning2001]

2001 • Groneberg and colleagues (Pulm Pharmacol Ther) review VIP as a mediator of asthma, the rationale for inhaled VIP/aviptadil drug development [groneberg2001]

2001 • Keijzers (Curr Opin Investig Drugs) reviews the aviptadil development program [keijzers2001]

2003 • Petkov and colleagues (J Clin Invest) report acute pulmonary vasodilation and chronic clinical improvement with inhaled aviptadil in a small uncontrolled trial in primary pulmonary hypertension [petkov2003]

2006 • Groneberg and colleagues (Eur J Pharmacol) review neuropeptide-based drug therapy with VIP and its receptors [groneberg2006]

2007 • Said (Peptides) publishes a retrospective on the discovery of VIP, 'initially looked for in the lung, isolated from intestine, identified as a neuropeptide' [said2007]

2007 • Onoue and colleagues (Peptides) review bioactive VIP analogues and drug-delivery systems for asthma/COPD [onoue2007]

2008 • Leuchte and colleagues (Eur Respir J) report single-dose hemodynamic effects of inhaled VIP in pulmonary hypertension [leuchte2008]

2008 • Dinsmore and Wyllie (BJU Int) review intracavernosal VIP/phentolamine (Invicorp) for erectile dysfunction, approved in several European countries, not FDA-approved [dinsmore2008]

2010 • Prasse and colleagues (Am J Respir Crit Care Med) report immunoregulatory effects of inhaled VIP in a Phase 1 study in pulmonary sarcoidosis [prasse2010]

2010 • Shoemaker and colleagues (Neurotoxicol Teratol) describe biomarkers including VIP in chronic biotoxin/inflammatory response syndromes, foundation for the CIRS observational protocol; no randomized controlled trial [shoemaker2010]

2012 • Harmar and colleagues (Br J Pharmacol) publish the IUPHAR review of VPAC1/VPAC2/PAC1 receptor pharmacology and functions [harmar2012]

2013 • Delgado and Ganea (Amino Acids) review VIP as a neuropeptide with pleiotropic immune functions [delgado2013]

2013 • Mathioudakis and colleagues (Hippokratia) review inhaled VIP agonists across respiratory therapeutics [mathioudakis2013]

2015 • Vosko and colleagues (Eur J Neurosci) review VIP in the suprachiasmatic nucleus light-input circadian system [vosko2015]

2017 • Belei and colleagues (Rom J Morphol Embryol) publish a literature review of Verner-Morrison syndrome, VIP-secreting tumors (VIPomas) and the WDHA syndrome [belei2017]

2019 • Iwasaki and colleagues (F1000Res) review recent advances in VIP physiology and pathophysiology with focus on the gastrointestinal system [iwasaki2019]

2022 • Youssef and colleagues (Crit Care Med) report on IV aviptadil in critical COVID-19 respiratory failure, the early ZYESAMI/RLF-100 clinical experience [youssef2022]

2023 • Brown and colleagues (Lancet Respir Med) report TESICO, multicenter randomized trial of IV aviptadil plus remdesivir vs remdesivir alone in hospitalized COVID-19 hypoxemic respiratory failure: no benefit; aviptadil ARDS development effectively halted [brown2023]

2025 • Udupa and colleagues (Indian J Crit Care Med) publish a systematic review and meta-analysis of aviptadil in ARDS, aggregate evidence does not support survival or oxygenation benefit [udupa2025]

Compounded Vasoactive Intestinal Peptide (VIP) (503A)

Physicians may submit patient-specific prescription requests for pharmacy review. For VIP, certain preparations may be available now when clinically appropriate, lawfully prescribed, and approved by the dispensing pharmacy. Availability is determined case by case and may depend on patient-specific documentation, ingredient status, source qualification, formulation feasibility, state requirements, and pharmacist judgment. The review starts with the evidence constraint: The evidence base for VIP includes endogenous physiology, aviptadil clinical studies, and foreign-product context, but no FDA-approved US

VIP or aviptadil product. Some US development programs did not meet approval standards, so patient-specific review must be cautious.

This ingredient is part of an evolving FDA review process. RonanRx is monitoring FDA's PCAC process and any subsequent agency action. This ingredient is part of an evolving FDA review process for peptide-related bulk substances used in compounding. Availability may change after FDA review, PCAC discussion, final agency action, or state-board guidance. For VIP, RonanRx ties that monitoring to the evidence limits described above and to any patient-specific documentation submitted by the prescriber.

Valid patient-specific prescription required. Supporting clinical rationale may be requested. Compounded medications are not FDA-approved. No consumer self-ordering, no office stock, no bulk dispensing. Requests for VIP are reviewed before any preparation is made or released. The legitimate path for VIP is not a protocol bought from an unregulated channel. It is a prescriber-submitted request reviewed by a licensed pharmacy against evidence, sourcing, sterile formulation, and patient-specific risk.

Vasoactive Intestinal Peptide (VIP) Formulations and Routes

Form	Concentration	Description
Synthetic VIP / aviptadil (research and clinical-trial supply)	—	Pharmaceutical-grade synthetic 28-amino-acid VIP, designated aviptadil when supplied as a pharmaceutical product, has been used in published clinical trials by inhalation (pulmonary hypertension, sarcoidosis), intravenous infusion (COVID-19 ARDS), and intracavernosal injection (erectile dysfunction, combined with phentolamine as Invicorp).
Invicorp (aviptadil + phentolamine intracavernosal injection)	—	Combination product approved for erectile dysfunction in several European countries; not FDA-approved in the U.S. The product combines synthetic VIP/aviptadil with phentolamine for intracavernosal administration.
Research peptide preparations (not commercial products)	—	Synthetic VIP is also available from peptide chemistry suppliers as a research-grade peptide. These preparations are not FDA-approved drug products and are not equivalent to pharmaceutical-grade clinical-trial supply.

Vasoactive Intestinal Peptide (VIP) Safety

Reported clinical safety experience with synthetic VIP/aviptadil is limited to small trials and one large multicenter randomized study in COVID-19 hypoxemic respiratory failure. The most consistently reported acute adverse events are dose-dependent systemic vasodilation effects, facial flushing, hypotension, and reflex tachycardia, particularly with intravenous administration; these reflect the peptide's primary

pharmacology [4][21][20]. The TESICO multicenter trial of IV aviptadil plus remdesivir vs remdesivir alone in hospitalized COVID-19 hypoxemic respiratory failure characterized adverse events in approximately 470 randomized participants and did not demonstrate clinical benefit on the primary respiratory recovery endpoint [21]; the 2025 systematic review and meta-analysis confirmed absence of survival or oxygenation benefit across the aviptadil ARDS trial corpus [22].

Inhaled VIP/aviptadil has been generally well tolerated in small uncontrolled or Phase 1 trials in pulmonary hypertension [7][10] and pulmonary sarcoidosis [12] with localized airway tolerability and short-term hemodynamic safety reported, but trial sizes are small and long-term safety in chronic respiratory indications is not characterized. The intracavernosal aviptadil/phentolamine combination (Invicorp, European approval) has documented intracavernosal-injection-class adverse events (transient facial flushing, headache, injection-site pain) [11].

Because VIP is on FDA's Category 2 bulk-substance list for 503A compounding [23], FDA has identified either safety concerns or an information gap that must be evaluated. Clinicians considering VIP-containing preparations from non-503A sources, including intranasal preparations used in the Shoemaker CIRS protocol, should be aware that such products are not subject to FDA bulk-substance review, USP <797> sterility standards, or pharmacist verification of identity and potency, and that the published evidence base for the CIRS indication is observational and weak [13]. Availability through RonanRx is determined case by case after pharmacy review.

Contraindications

Honest gap. No FDA-approved U.S. VIP product exists, so no FDA-defined contraindications. Published trial protocols typically excluded patients with severe hemodynamic instability, profound hypotension, or known hypersensitivity to the peptide or excipients. The European Invicorp label (intracavernosal aviptadil/phentolamine for erectile dysfunction) contraindicates use in patients with predisposition to priapism and certain hematologic conditions. FDA Category 2 bulk-substance status precludes 503A compounding pending reclassification.

Searched: PubMed, DailyMed, FDA bulk-substance review documents on 2026-05-11 · terms *vasoactive intestinal peptide OR aviptadil AND (contraindication OR contraindicated OR hypersensitivity)*.

Drug interactions

Honest gap. No formal published drug-interaction studies for VIP/aviptadil are indexed at the time of review. Pharmacodynamic interaction with other vasodilators (nitrates, phosphodiesterase-5 inhibitors, prostacyclin analogues) is theoretical given the peptide's systemic vasodilator effects; no clinical interaction studies have been published.

Searched: PubMed, DailyMed on 2026-05-11 · terms *vasoactive intestinal peptide OR aviptadil AND (drug interaction OR pharmacokinetic interaction)*.

Adverse events

Across published clinical trials, the most consistently reported VIP/aviptadil adverse events are acute systemic-vasodilation-class events: facial flushing, hypotension, and reflex tachycardia, predominantly with intravenous administration [21][20][4]. The TESICO multicenter trial in COVID-19 hypoxemic respiratory failure [21] characterized adverse events in approximately 470 randomized participants and did not demonstrate clinical benefit on the primary respiratory recovery endpoint [21]; the 2025 systematic review and meta-analysis confirmed no survival or oxygenation benefit across the aviptadil ARDS corpus [22]. Inhaled VIP/aviptadil has been generally well tolerated in small uncontrolled or Phase 1 trials in pulmonary hypertension [7][10] and pulmonary sarcoidosis [12], with short-term safety reported but trial sizes too small to characterize uncommon events.

Intracavernosal aviptadil/phentolamine (Invicorp, European approval) has documented class-typical adverse events for intracavernosal-injection ED therapy, transient facial flushing, headache, and injection-site pain, without the priapism rate associated with selective α-adrenergic intracavernosal therapies [11].

Monitoring Vasoactive Intestinal Peptide (VIP) Therapy

No RonanRx-specific monitoring protocol has been established for VIP. If a patient-specific prescription is submitted, supporting clinical rationale may be requested, and monitoring expectations would be reviewed case by case against the published evidence, route, sterile or nonsterile status, concomitant therapies, and patient risk factors.

Vasoactive Intestinal Peptide (VIP) in Special Populations

Vasoactive Intestinal Peptide (VIP) Evidence Quality

The VIP physiologic and preclinical evidence base is broad and biologically coherent. The peptide is established as an endogenous neuropeptide with vasodilator, smooth-muscle-relaxant, immunomodulatory, and neurotransmitter roles, signaling through the VPAC1/VPAC2 receptors shared with PACAP [bodanszky1974; said2007; harmar2012]. The clinical drug-development evidence base for synthetic VIP/aviptadil, however, is small in absolute terms and dominated by negative or inconclusive late-stage results.

Pulmonary arterial hypertension. Published inhaled aviptadil evidence consists of small open-label or uncontrolled trials [petkov2003] reporting acute pulmonary vasodilation and short-term clinical signal; no large randomized confirmatory trial has been published and most development was discontinued [petkov2003, leuchte2008, mathioudakis2013]. Pulmonary sarcoidosis. The Prasse 2010 Phase 1 inhaled-VIP trial reported immunoregulatory and symptomatic signal in a small sample without progression to a

confirmatory program [prasse2010]. COVID-19 hypoxemic respiratory failure. The TESICO multicenter randomized trial [brown2023] of IV aviptadil plus remdesivir vs remdesivir alone reported no benefit on the primary respiratory recovery endpoint [brown2023]; the Youssef 2022 single-center report described the prior ZYESAMI/RLF-100 clinical experience [youssef2022]; the Udupa 2025 systematic review and meta-analysis confirmed absence of survival or oxygenation benefit across the aviptadil ARDS corpus [udupa2025]. Erectile dysfunction. Intracavernosal aviptadil/phentolamine (Invicorp) is approved in several European countries on the basis of multiple controlled trials [dinsmore2008, keijzers2001]; the product is not FDA-approved and intracavernosal ED compounding is outside RonanRx's scope. CIRS / Shoemaker protocol [delgado2013; iwasaki2019; vosko2015]. Use of intranasal VIP within the chronic-inflammatory-response-syndrome protocol described by Shoemaker and colleagues is supported by observational case-series and biomarker data without randomized controlled trials [shoemaker2010]; the evidence is honestly characterized as weak [saidmutt1972; henning2001].

Regulatory and compounding considerations dominate the access question for U.S. patients. VIP is on FDA's Category 2 bulk-substance list for 503A compounding [fda_cat2_peptides]. There is no FDA-approved U.S. product. The pharmacovigilance, sterility-assurance, and identity-verification framework that legitimate 503A compounding provides is therefore unavailable for VIP under current FDA designation, and Physicians may submit patient-specific prescription requests for pharmacy review. Availability is determined case by case. Any clinical use in U.S. adults at the time of this review (2026-05-11) is outside the FDA bulk-substance review and outside RonanRx's quality and traceability standards.

Major Vasoactive Intestinal Peptide (VIP) Clinical Studies

Study	Design	Participants	Duration	Finding
Said and Mutt (1972, Eur J Biochem), VIP isolation and sequence	Biochemical isolation from porcine intestinal wall; structural determination	—	—	Isolation of a vasoactive 28-residue octacosapeptide related to secretin and glucagon, the canonical VIP isolation paper [saidmutt1972]
Bodanszky, Klausner, and Lin (1974, J Am Chem Soc), Total synthesis	Solid-phase chemical synthesis	—	—	First total chemical synthesis of the 28-residue VIP molecule, enabling pharmacologic and clinical investigation [bodanszky1974]
Said (2007, Peptides), Discovery retrospective	Historical narrative review by the discoverer	—	—	Summarizes the discovery sequence, VIP was 'initially looked for in the lung, isolated

Study	Design	Participants	Duration	Finding
				from intestine, and identified as a neuropeptide' [said2007]
Henning and Sawmiller (2001, Cardiovasc Res), Cardiovascular effects	Comprehensive narrative review	—	—	Summarizes systemic and pulmonary vasodilation, coronary vasodilation, and inotropic/chronotropic effects of VIP across animal models and human physiology [henning2001]
Groneberg et al. (2001, Pulm Pharmacol Ther), VIP in asthma	Narrative review	—	—	Articulates the rationale for VIP and inhaled VIP analogue development in asthma, bronchial smooth-muscle relaxation, airway anti-inflammatory effects [groneberg2001]
Petkov et al. (2003, J Clin Invest), Inhaled aviptadil in PAH	Small uncontrolled trial of single-dose and short-term repeated inhaled aviptadil in adults with primary pulmonary hypertension	8	—	Acute reduction in pulmonary vascular resistance and improvement in 6-minute walk distance over 3 months in a small uncontrolled cohort, the foundational positive PAH signal that motivated subsequent inhaled-VIP development [petkov2003]
Groneberg et al. (2006, Eur J Pharmacol), VIP neuropeptide drug therapy	Narrative review	—	—	Reviews novel neuropeptide-based drug therapy concepts with VIP and its receptors across respiratory, gastrointestinal, and inflammatory indications [groneberg2006]
Onoue et al. (2007, Peptides), Bioactive analogues and drug delivery	Narrative review	—	—	Summarizes VIP analogue medicinal chemistry and inhaled and parenteral drug-delivery systems developed for asthma and COPD [onoue2007]
Dinsmore and Wyllie (2008, BJU	Narrative review of the aviptadil/phentolamine	—	—	Synthesizes the controlled-trial evidence base supporting

Study	Design	Participants	Duration	Finding
Int), Intracavernosal VIP/phentolamine for ED	intracavernosal program (Invicorp)			European approval of intracavernosal aviptadil/ phentolamine for erectile dysfunction; product is not FDA-approved in the U.S [dinsmore2008].
Leuchte et al. (2008, Eur Respir J), Inhaled VIP in pulmonary hypertension	Single-dose hemodynamic study of inhaled VIP in adults with pulmonary hypertension	—	—	Acute reduction in pulmonary vascular resistance with inhaled VIP; small sample, no long-term efficacy claim [leuchte2008]
Prasse et al. (2010, Am J Respir Crit Care Med), Inhaled VIP in pulmonary sarcoidosis	Phase 1 study of inhaled VIP in adults with pulmonary sarcoidosis	—	—	Inhaled VIP exerted immunoregulatory effects (reduced TNF-α from alveolar macrophages; increased regulatory T cell signal) with short-term tolerability; small sample without progression to a confirmatory program [prasse2010]
Harmar et al. (2012, Br J Pharmacol), VPAC/ PAC1 receptor pharmacology	IUPHAR receptor-nomenclature review	—	—	Systematizes the pharmacology and functions of VPAC1, VPAC2, and PAC1 receptors shared by VIP and PACAP, the canonical reference for VIP receptor signaling [harmar2012]
Delgado and Ganea (2013, Amino Acids), Pleiotropic immune functions	Comprehensive narrative review	—	—	Summarizes VIP as an endogenous anti-inflammatory neuropeptide with effects on macrophage polarization, Th cell balance, regulatory T cells, and NF-κB-driven cytokine transcription [delgado2013]
Mathioudakis et al. (2013, Hippokratia), Inhaled VIP agonists	Narrative review of inhaled VIP across respiratory indications	—	—	Synthesizes the inhaled-VIP literature in asthma, COPD, pulmonary hypertension, and sarcoidosis; signals are positive in small trials with no large

Study	Design	Participants	Duration	Finding
				confirmatory program [mathioudakis2013]
Vosko et al. (2015, Eur J Neurosci), VIP in circadian system	Narrative review	—	—	Characterizes VIP's role in the suprachiasmatic nucleus light-input pathway and circadian rhythm coordination [vosko2015]
Belei et al. (2017, Rom J Morphol Embryol), Verner-Morrison syndrome	Literature review of VIPoma and the WDHA syndrome	—	—	Summarizes clinical, biochemical, and pathologic features of VIP-secreting neuroendocrine tumors, the pathologic counterpart that established VIP's physiologic GI secretory role [belei2017]
Iwasaki et al. (2019, F1000Res), Recent advances in VIP physiology	Narrative review with focus on the GI system	—	—	Updates VIP physiology and pathophysiology with emphasis on gastrointestinal motility, secretion, and inflammatory regulation [iwasaki2019]
Youssef et al. (2022, Crit Care Med), IV aviptadil in critical COVID-19	Single-center clinical report of IV aviptadil in critically ill COVID-19 respiratory failure patients (ZYESAMI/ RLF-100 clinical experience)	—	—	Described early experience with IV aviptadil in critical COVID-19; foundational clinical-experience report leading into the multicenter randomized program [youssef2022]
Brown et al. (2023, Lancet Respir Med), TESICO trial	Multicenter randomized double-blind placebo-controlled trial of IV aviptadil plus remdesivir vs remdesivir alone in hospitalized COVID-19 hypoxemic respiratory failure (ACTIV-3b)	471	—	IV aviptadil plus remdesivir did not improve the primary respiratory recovery endpoint compared with remdesivir alone, the largest randomized VIP/ aviptadil trial reported to date; effectively halted U.S [brown2023]. ARDS development
Udupa et al. (2025, Indian J Crit Care Med), Aviptadil in	Systematic review and meta-analysis of aviptadil clinical trials in ARDS	—	—	Aggregate evidence across the aviptadil ARDS trial corpus does not support survival or oxygenation benefit [udupa2025]

Study	Design	Participants	Duration	Finding
ARDS meta-analysis				
Shoemaker et al. (2010, Neurotoxicol Teratol), Biotoxin biomarker work	Observational case-series characterizing biomarkers including VIP in chronic biotoxin-associated inflammatory illness	—	—	Established VIP as one biomarker in the chronic-inflammatory-response-syndrome framework; foundation for the observational Shoemaker protocol, no randomized controlled trial of intranasal VIP exists [shoemaker2010]

Vasoactive Intestinal Peptide (VIP) Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

VIP is a 28-amino-acid peptide rapidly catabolized in plasma and tissue by peptidases, with reported plasma half-lives in the order of 1, 2 minutes after intravenous administration. Synthetic-peptide pharmacokinetic characterization for aviptadil has been performed in the context of clinical-trial development for pulmonary hypertension, ARDS, and intracavernosal ED therapy; published comprehensive PK profiles for VIP/aviptadil are limited and indication-specific, and there is no FDA-approved label that consolidates a U.S. PK section.

Inhaled aviptadil delivers peptide directly to the pulmonary vasculature with relatively selective pulmonary vasodilation reported in pulmonary hypertension trials [petkov2003, leuchte2008]. Intravenous aviptadil produces systemic vasodilation with the corresponding hemodynamic adverse-event profile (flushing, hypotension, reflex tachycardia) [brown2023, youssef2022]. Intracavernosal aviptadil/phentolamine acts locally on cavernosal smooth muscle with limited systemic exposure [dinsmore2008].

Pharmacodynamics

Reported pharmacodynamic effects of synthetic VIP/aviptadil include: dose-dependent reduction in pulmonary vascular resistance and modest systemic vasodilation (cardiovascular endpoints); bronchial smooth-muscle relaxation and airway anti-inflammatory effects (respiratory endpoints); immunomodulation of macrophage polarization and Th cell balance (immune endpoints) [delgado2013, prasse2010]; gastrointestinal smooth-muscle relaxation and secretory effects (the WDHA syndrome physiology of VIPoma confirms the GI secretory role) [belei2017, iwasaki2019]; and corpus cavernosum smooth-muscle relaxation supporting erectile response (intracavernosal therapy) [dinsmore2008] [groneberg2001; groneberg2006; onoue2007; mathioudakis2013].

Vasoactive Intestinal Peptide (VIP) Compounding & Operations

503A compounding

Physicians may submit patient-specific prescription requests for pharmacy review. For VIP, certain preparations may be available now when clinically appropriate, lawfully prescribed, and approved by the dispensing pharmacy. Availability is determined case by case and may depend on patient-specific documentation, ingredient status, source qualification, formulation feasibility, state requirements, and pharmacist judgment. The review starts with the evidence constraint: The evidence base for VIP includes endogenous physiology, aviptadil clinical studies, and foreign-product context, but no FDA-approved US VIP or aviptadil product. Some US development programs did not meet approval standards, so patient-specific review must be cautious.

This ingredient is part of an evolving FDA review process. RonanRx is monitoring FDA's PCAC process and any subsequent agency action. This ingredient is part of an evolving FDA review process for peptide-related bulk substances used in compounding. Availability may change after FDA review, PCAC discussion, final agency action, or state-board guidance. For VIP, RonanRx ties that monitoring to the evidence limits described above and to any patient-specific documentation submitted by the prescriber.

Valid patient-specific prescription required. Supporting clinical rationale may be requested. Compounded medications are not FDA-approved. No consumer self-ordering, no office stock, no bulk dispensing. Requests for VIP are reviewed before any preparation is made or released. The legitimate path for VIP is not a protocol bought from an unregulated channel. It is a prescriber-submitted request reviewed by a licensed pharmacy against evidence, sourcing, sterile formulation, and patient-specific risk.

Pharmacist review

For VIP, the pharmacist review starts before any preparation is made. Valid patient-specific prescription required. Supporting clinical rationale may be requested. The pharmacist reviews ingredient status, sourcing, formulation feasibility, state requirements, patient-specific documentation, and whether dispensing is appropriate case by case.

Quality and traceability

If a VIP preparation is approved after pharmacy review, RonanRx applies source documentation, formulation records, lot traceability, release checks, and storage controls appropriate to the actual dosage form. Research-use vial storage practices do not substitute for pharmacy-assigned storage, beyond-use dating, sterility controls when applicable, or recallable batch records. The patient-specific framework and quality controls are documented in the cited compounding references [fda503a; usp_795; usp_797].

Cold chain

If a VIP preparation is approved after pharmacy review, RonanRx applies source documentation, formulation records, lot traceability, release checks, and storage controls appropriate to the actual dosage form. Research-use vial storage practices do not substitute for pharmacy-assigned storage, beyond-use dating, sterility controls when applicable, or recallable batch records.

Frequently Asked Questions About Vasoactive Intestinal Peptide (VIP)

Can physicians request VIP through RonanRx?

Physicians may submit patient-specific prescription requests for pharmacy review. Certain preparations may be available now when clinically appropriate, lawfully prescribed, and approved by the dispensing pharmacy. Availability is determined case by case. Compounded medications are not FDA-approved, and no consumer self-ordering, office stock, or bulk dispensing is offered.

What is VIP?

Vasoactive intestinal peptide is a 28-amino-acid endogenous neuropeptide of the secretin/glucagon/PACAP superfamily, discovered by Sami Said and Viktor Mutt in 1970 in porcine intestinal extracts [saidmutt1972; said2007; harmar2012]. It signals through the VPAC1 and VPAC2 receptors with downstream cAMP elevation and produces vasodilation, smooth-muscle relaxation, immune modulation, and neurotransmission in autonomic, enteric, and central pathways [henning2001].

Is aviptadil the same as VIP?

Aviptadil is the pharmaceutical-grade synthetic 28-residue VIP peptide supplied as a drug product [bodanszky1974]. The amino-acid sequence is identical to endogenous human VIP. The name aviptadil is used in regulatory and clinical-trial contexts; 'VIP' is used in biology and pharmacology more broadly [keijzers2001].

Is there an FDA-approved VIP product in the U.S.?

No. There is no FDA-approved VIP or aviptadil product in the United States. In several European countries the intracavernosal combination product Invicorp (aviptadil + phentolamine) is authorized for erectile dysfunction [dinsmore2008]. The U.S. aviptadil ARDS/COVID-19 program (ZYESAMI/RLF-100) did not meet its primary endpoint in the TESICO multicenter trial and was not approved [keijzers2001; brown2023; udupa2025].

What about VIP for chronic inflammatory response syndrome (CIRS / Shoemaker protocol)?

For VIP, physicians may submit patient-specific prescription requests for pharmacy review. Availability is determined case by case, and supporting clinical rationale may be requested.

Did inhaled VIP work for pulmonary hypertension or sarcoidosis?

Small uncontrolled or Phase 1 trials reported short-term hemodynamic and immunoregulatory signal with inhaled VIP/aviptadil in primary pulmonary hypertension (Petkov 2003; Leuchte 2008) and in pulmonary sarcoidosis (Prasse 2010) [petkov2003; leuchte2008; prasse2010]. No large randomized confirmatory trial has been published in either indication and most U.S. development was discontinued [mathioudakis2013].

What is a VIPoma?

A VIPoma is a rare VIP-secreting neuroendocrine tumor, most often pancreatic, that produces the Verner-Morrison syndrome (also called WDHA syndrome: watery diarrhea, hypokalemia, achlorhydria) by sustained pathologic VIP secretion [belei2017]. The syndrome is the pathologic counterpart that established VIP's normal physiologic role in gastrointestinal motility and secretion [iwasaki2019].

Could VIP move from FDA Category 2 to Category 1?

Possibly, if the agency receives sufficient evidence to evaluate safety and clinical utility. The Category 2 designation reflects FDA's current assessment of the evidence base; it is not a permanent finding. RonanRx will track future bulk-substance review revisions and will reconsider compounding only if and when VIP is moved to Category 1 [fda_cat2_peptides].

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How to Access Vasoactive Intestinal Peptide (VIP)

Compounded Vasoactive Intestinal Peptide (VIP) is dispensed under 503A on a patient-specific prescription. Depending on your role, the next step looks different.

FOR PRESCRIBING CLINICIANS

Offer this medication

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

ronanrx.com/request-partnership-call

PATIENT WITH A DOCTOR

Receive your prescription

If your doctor has prescribed Vasoactive Intestinal Peptide (VIP), sign up so we can prepare and ship your medication. The signup wizard collects intake and connects you to the prescribing workflow.

ronanrx.com/patients

PATIENT WITHOUT A DOCTOR

Find a partner clinic

RonanRx prescribes through partner clinics — we don't initiate prescriptions on this site. Read how the referral process works and how to find a partner clinic in your state.

ronanrx.com/find-clinic

Other compounds RonanRx makes

This monograph is one of many in the RonanRx formulary. Every compound below is prepared under 503A on a patient-specific prescription. Browse the full catalog at ronanrx.com/medications and ronanrx.com/peptides, or scan the codes at right for each index.

Medications

Peptides

MEDICATIONS (40)

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

PEPTIDES (21)

Sermorelin — Available now

Tesamorelin — Available now

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

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

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

Hexarelin — Growth-hormone axis (under FDA review)

Ipamorelin — Growth-hormone axis (under FDA review)

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

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

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

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

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

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

Selank — Neuro & cognitive (under FDA review)

Semax — Neuro & cognitive (under FDA review)

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

BPC-157 — Tissue repair (under FDA review)

KPV — Tissue repair (under FDA review)

LL-37 — Tissue repair (under FDA review)

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

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