

## RESEARCH MONOGRAPH . COMPOUND PROFILE

# Selepressin

*A synthetic nonapeptide vasopressin analog developed at Ferring Pharmaceuticals as a potent, highly selective, short-acting full agonist of the vasopressin type 1a receptor, designed to replicate the vasoconstrictive hemodynamic support of arginine vasopressin in septic shock while eliminating V2-receptor-mediated antidiuretic, procoagulant, and fluid-retaining liabilities.*

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## ABSTRACT

Selepressin (FE 202158; [Phe(2),Ile(3),Hgn(4),Orn(iPr)(8)]vasopressin; CAS 876296-47-8; molecular formula C<sub>46</sub>H<sub>73</sub>N<sub>13</sub>O<sub>11</sub>S<sub>2</sub>; molecular weight 1048.29) is a synthetic nonapeptide analog of arginine vasopressin (AVP) and a potent, selective, short-acting full agonist of the human vasopressin type 1a receptor (V1aR), developed by Ferring Pharmaceuticals for the treatment of vasodilatory hypotension in septic shock. The compound was identified through a systematic structure-activity relationship campaign at the Ferring Research Institute in San Diego, in which modifications at positions 2, 4, and 8 of the vasopressin backbone were explored to dissociate V1a-mediated vasoconstriction from the V2-receptor-mediated antidiuresis, V1b-mediated corticotropin release, and oxytocin-receptor-mediated uterotonic effects that complicate clinical AVP administration [1, 2]. Selepressin activates the human V1a receptor with an EC<sub>50</sub> of 2.4 nanomolar in functional assays, producing a selectivity ratio of 1:142:1107:440 relative to V1b, V2, and oxytocin receptors, respectively [2]. This selectivity profile confers three pharmacological advantages over AVP in the septic shock setting: absence of V2-receptor-mediated free water retention and consequent fluid overload; absence of V2-receptor-mediated release of von Willebrand factor and consequent procoagulant risk [3]; and absence of V2-receptor-mediated exacerbation of capillary leak through endothelial aquaporin-2 trafficking. Preclinical pharmacology in ovine fecal peritonitis, ovine *Pseudomonas aeruginosa* pneumonia, canine hemodynamic, and rabbit endotoxemia models demonstrated that selepressin maintains mean arterial pressure comparably to AVP, reduces

cumulative fluid requirements, attenuates pulmonary edema, preserves mesenteric perfusion more favorably than AVP, and improves survival relative to both AVP and norepinephrine when administered early in the septic course [4, 5, 6, 7]. In vitro, selepressin protects human lung microvascular endothelial barrier integrity against thrombin, vascular endothelial growth factor, angiopoietin-2, and lipopolysaccharide challenge through V1a-receptor-dependent activation of p53, suppression of RhoA/myosin light chain 2 signaling, and activation of the Rac1 GTPase barrier-protective pathway [8]. A Phase IIa randomized, double-blind, placebo-controlled trial in 53 patients with early septic shock (Russell et al. 2017) demonstrated that selepressin at 2.5 nanograms per kilogram per minute effectively substituted for norepinephrine, reduced 7-day cumulative norepinephrine dose from 761 to 249 micrograms per kilogram, lowered cumulative net fluid balance from day 5 onward, and increased ventilator-free days [9]. The pivotal SEPSIS-ACT adaptive Phase 2b/3 randomized clinical trial (Laterre et al. 2019, JAMA) enrolled 868 adults with septic shock across 63 hospitals in Belgium, Denmark, France, the Netherlands, and the United States. Three selepressin dosing regimens (starting infusion rates of 1.7, 2.5, and 3.5 nanograms per kilogram per minute) were compared to placebo. The trial was stopped for futility at the completion of Part 1: the primary endpoint of ventilator- and vasopressor-free days within 30 days was 15.0 days with selepressin versus 14.5 days with placebo (difference 0.6 days; 95 percent confidence interval, negative 1.3 to 2.4; P equals 0.30), and 90-day mortality was 40.6 percent versus 39.4 percent [10]. Selepressin did produce statistically significant reductions in cardiovascular Sequential Organ Failure Assessment score at 24 hours (difference negative 0.42; P less than 0.001) and in hourly fluid balance at 24 hours (81

versus 107 milliliters per hour; P less than 0.001), confirming the hemodynamic and fluid-sparing pharmacodynamic effects observed in Phase IIa. The compound is not approved by any regulatory authority. It is available from chemical suppliers as a research-grade peptide. This monograph reviews the chemistry and structure-activity relationships, the receptor pharmacology and selectivity, the comprehensive preclinical evidence base across multiple sepsis models, the human pharmacokinetic profile, the Phase IIa and Phase 2b/3 clinical evidence, sourcing and reconstitution considerations, stack-interaction implications, adverse-event signal, and a comparative assessment of five vasopressor alternatives on five competency standards.

# 1. Compound Identification

## 1.1 Names, synonyms, and registry identifiers

**International Nonproprietary Name:** Selepressin (proposed; not formally assigned by the World Health Organization at the time of monograph preparation).

**Development code:** FE 202158 (Ferring Pharmaceuticals). The development code is the canonical identifier in the early medicinal chemistry and pharmacology literature and the identifier under which the seminal Laporte et al. (2011) pharmacological characterization and Wisniewski et al. (2011) structure-activity relationship reports were published [1, 2].

**Chemical Abstracts Service registry number:** 876296-47-8 (free base). No separate hydrochloride or acetate salt CAS number has been assigned in the primary literature; the compound is typically supplied as the trifluoroacetate or acetate salt from peptide synthesis.

**International Union of Pure and Applied Chemistry name:** The compound is a modified nonapeptide and is designated by the substitution nomenclature [Phe(2),Ile(3),Hgn(4),Orn(iPr)(8)]vasopressin, indicating phenylalanine at position 2, isoleucine at position 3, homoglutamine at position 4, and N-isopropyl-ornithine at position 8 of the arginine vasopressin backbone.

**PubChem CID:** 53330936.

**ChemSpider ID:** 26609297.

**Unique Ingredient Identifier (UNII):** 8P2T76M0SJ.

**ChEMBL ID:** ChEMBL1817709.

## 1.2 Structural class and chemistry

Selepressin is a synthetic nonapeptide (nine amino acid residues) and a structural analog of arginine vasopressin (AVP, antidiuretic hormone). Like AVP, selepressin contains a 20-membered disulfide-bridged cyclic ring formed by a cysteine-cysteine disulfide bond between positions 1 and 6, with a linear tripeptide tail at posi-

tions 7 through 9 terminating in a glycine. The compound retains the overall vasopressin topological framework but incorporates four amino acid substitutions that were systematically optimized through structure-activity relationship studies at the Ferring Research Institute to achieve selectivity for the V1a receptor over the V1b, V2, and oxytocin receptors [1].

**Molecular formula:** C<sub>46</sub>H<sub>73</sub>N<sub>13</sub>O<sub>11</sub>S<sub>2</sub> (free base).

**Molecular weight:** 1048.29 g/mol (free base, calculated).

**Physical properties:** White to off-white lyophilized powder. Soluble in water, dimethyl sulfoxide, and dilute acetic acid; sparingly soluble in apolar organic solvents. The compound is hygroscopic and should be stored desiccated.

**Stereochemistry:** All amino acid residues in selepressin are in the L-configuration, consistent with the parent vasopressin backbone. The disulfide bridge between Cys-1 and Cys-6 constrains the macrocyclic ring and is essential for receptor binding; reduction of the disulfide abolishes V1a agonist activity.

## 1.3 Synthesis

Selepressin is prepared by solid-phase peptide synthesis using standard 9-fluorenylmethyloxycarbonyl (Fmoc) chemistry on a peptide synthesizer. The synthetic sequence assembles the linear precursor on a Rink amide resin (to generate the C-terminal glycine), with sequential coupling of protected amino acids in the C-to-N direction. The nonstandard residues (homoglutamine at position 4, N-isopropyl-ornithine at position 8) are prepared as Fmoc-protected building blocks prior to incorporation [1]. After assembly of the linear nonapeptide, cleavage from the resin with trifluoroacetic acid and simultaneous side-chain deprotection yields the crude linear peptide. Cyclization is achieved by oxidative disulfide formation between the cysteine residues at positions 1 and 6, typically using air oxidation in dilute aqueous solution at pH 7 to 8 or by iodine oxidation. The crude cyclic peptide is purified by reversed-phase high-performance liquid chromatography (RP-HPLC) and characterized by electrospray ionization mass spectrometry, analytical RP-HPLC, and amino acid analysis. The final product is lyophilized as the trifluoroacetate salt (from HPLC mobile phase) or converted to the acetate salt by ion exchange. Industrial-scale synthesis achieves purities greater than 95 percent by HPLC area percent. A bioanalytical method for quantification of selepressin in hu-

man plasma at low picogram-per-milliliter concentrations using coupled-column liquid chromatography-tandem mass spectrometry was reported by Lovgren et al. (2010) [11].

## 2. Abstract

Selepressin (FE 202158) is a synthetic nonapeptide vasopressin analog and a potent, selective, short-acting full agonist of the vasopressin type 1a receptor (V1aR), developed by Ferring Pharmaceuticals as a vasopressor for the treatment of vasodilatory hypotension in septic shock [1, 2]. The compound activates the human V1a receptor with an EC<sub>50</sub> of 2.4 nanomolar and demonstrates a selectivity ratio of 1:142:1107:440 relative to the V1b, V2, and oxytocin receptors, respectively [2]. This selectivity profile distinguishes selepressin from arginine vasopressin, which activates all four receptor subtypes at clinically relevant concentrations, and from terlipressin, which retains substantial V2 activity.

The rationale for V1a selectivity in septic shock derives from the recognition that V2-receptor activation by exogenous vasopressin produces three categories of harm in the critically ill: free water retention through renal collecting duct aquaporin-2 insertion, which exacerbates the positive fluid balance that independently predicts mortality in septic shock; release of von Willebrand factor from endothelial Weibel-Palade bodies, which promotes microvascular thrombosis in the setting of disseminated intravascular coagulation [3]; and potentiation of endothelial barrier dysfunction through mechanisms that remain under investigation. Selepressin, by activating only the V1a receptor at therapeutic concentrations, preserves the vasoconstrictive hemodynamic support of vasopressin while eliminating these V2-mediated liabilities.

Preclinical evidence in ovine septic shock models demonstrated that selepressin maintains mean arterial pressure, reduces cumulative fluid requirements, attenuates pulmonary edema, and improves survival relative to both arginine vasopressin and norepinephrine [4, 5, 6]. In vitro studies confirmed that selepressin protects human lung microvascular endothelial barrier integrity through V1a-receptor-dependent signaling involving p53 activation and Rac1 GTPase engagement [8].

Clinical development included a Phase IIa trial in 53 septic shock patients (Russell et al. 2017) demonstrating effective norepinephrine substitution at the 2.5 nanogram per kilogram per minute dose [9], followed by the pivotal SEPSIS-ACT adaptive Phase 2b/3 trial in 868 patients (Laterre et al. 2019) which was stopped for futility on the primary endpoint of ventilator- and vasopressor-free days, despite

demonstrating significant short-term hemodynamic and fluid-balance benefits [10]. The compound is not approved by any regulatory authority and is not in active clinical development. It remains available as a research-grade peptide and serves as the reference compound for selective V1a receptor agonism in critical care pharmacology.

## 3. Discovery and Development History

### 3.1 Origin and medicinal chemistry

Selepressin was discovered at the Ferring Research Institute in San Diego, California, through a systematic structure-activity relationship program directed at producing vasopressin analogs with high selectivity for the V1a receptor. The program was motivated by the landmark Vasopressin and Septic Shock Trial (VASST), published by Russell et al. in the New England Journal of Medicine in 2008, which demonstrated that low-dose arginine vasopressin (0.03 units per minute) added to norepinephrine in septic shock reduced norepinephrine requirements and showed a 90-day mortality benefit in the less-severe septic shock subgroup [12]. However, clinical AVP activates all four vasopressin and oxytocin receptor subtypes, and the V2-mediated antidiuretic, procoagulant, and fluid-retaining effects were recognized as potential liabilities that might offset the V1a-mediated hemodynamic benefit.

Wisniewski et al. (2011) reported the medicinal chemistry campaign in the Journal of Medicinal Chemistry [1]. The design strategy employed the general framework [Xaa(2),Ile(3),Yaa(4),Zaa(8)]vasopressin, systematically varying amino acid substituents at positions 2, 4, and 8 while retaining isoleucine at position 3 (the same residue as in lypressin, the porcine vasopressin). Modifications at position 2 (phenylalanine replacing tyrosine) eliminated the hydroxyl group critical for V2 receptor activation. Modifications at position 4 (homoglutamine replacing glutamine) and position 8 (N-isopropyl-ornithine replacing arginine) further shifted selectivity toward V1a. Compound 45 in the Wisniewski series, designated FE 202158, emerged as the lead compound on the basis of potency, selectivity, short duration of action comparable to AVP, and favorable pharmacokinetic properties in rats.

### 3.2 Pharmacological characterization

Laporte et al. (2011) published the comprehensive pharmacological characterization of FE 202158 in the Journal of Pharmacology and Experimental Therapeutics [2]. The study established the V1a EC<sub>50</sub> of 2.4 nanomolar, the selectivity ratios across the four receptor subtypes, and the in vivo vasoconstrictor potency in rat ear skin blood flow assays (ED<sub>50</sub> of 4.0 picomoles per kilogram per minute, comparable

to AVP at 3.4 picomoles per kilogram per minute). Critically, FE 202158 produced no measurable antidiuretic activity at vasopressor doses, confirming the functional dissociation of V1a vasoconstriction from V2 antidiuresis.

### 3.3 Preclinical sepsis programs

Between 2012 and 2020, three principal preclinical programs extended the pharmacological characterization to sepsis and shock models. Maybauer et al. (2014) at the University of Texas Medical Branch demonstrated in chronically instrumented sheep with *Pseudomonas aeruginosa* pneumonia and smoke inhalation injury that selepressin almost completely blocked the approximately 7 liters of pathological fluid accumulation observed in untreated septic controls, whereas AVP only partially reduced it [5]. Importantly, addition of the V2 agonist desmopressin to selepressin restored fluid accumulation to levels similar to AVP, directly implicating V2 receptor activation in the pathological fluid retention. He et al. (2016) at the Universite Libre de Bruxelles demonstrated in ovine fecal peritonitis that selepressin maintained mean arterial pressure and cardiac index better than AVP or norepinephrine, produced lower interleukin-6 and nitrite/nitrate levels, and significantly prolonged survival, with the greatest benefit observed in early-intervention protocols [4].

### 3.4 Clinical development

Clinical development proceeded in two stages. The Phase IIa trial (NCT01000649, Russell et al. 2017) enrolled 53 patients with early septic shock across multiple centers and established the 2.5 nanogram per kilogram per minute dose as the pharmacodynamically optimal regimen [9]. The SEPSIS-ACT adaptive Phase 2b/3 trial (NCT02508649, Lewis et al. 2018 design paper, Laterre et al. 2019 results) received FDA Special Protocol Assessment agreement and enrolled 868 patients across 63 hospitals between July 2015 and August 2017 [10, 13]. The trial employed Bayesian response-adaptive randomization in Part 1 to select the optimal dosing regimen from three candidates (1.7, 2.5, and 3.5 nanograms per kilogram per minute) before a planned Part 2 confirmatory phase with a minimum of 1000 patients. The trial was stopped for futility at the completion of Part 1: no dosing regimen achieved a prespecified probability threshold for success on the primary endpoint of ventilator- and vasopressor-free days within 30 days. The planned highest dosing arm (5.0 nanograms per kilogram per minute) was never initiated.

### 3.5 Current status

Selepressin is not approved by any regulatory authority. Following the SEPSIS-ACT futility determination, Ferring Pharmaceuticals discontinued active clinical development. The compound is not in active commercial development for any indication. It persists in the critical care research literature as the canonical selective V1a receptor agonist and as a reference compound for preclinical and translational studies of vasopressin receptor pharmacology in shock states. Commentary by Asfar et al. (2016) in *Critical Care Medicine* characterized the development program as a step toward "decatecholaminization" of septic shock management [14].

## 4. Mechanism of Action

Selepressin is a selective, potent, short-acting full agonist of the vasopressin type 1a receptor. Its principal molecular activity, characterized in heterologous expression systems and confirmed in native tissue, animal models, and human clinical pharmacodynamics, is activation of V1a-receptor-mediated vasoconstriction and endothelial barrier stabilization without activation of the V1b, V2, or oxytocin receptors at therapeutic concentrations.

### 4.1 V1a receptor agonism

The vasopressin type 1a receptor (V1aR, also designated AVPR1A) is a G-protein-coupled receptor of the rhodopsin family expressed on vascular smooth muscle cells, hepatocytes, platelets, and the myometrium. Activation of V1aR by its endogenous ligand arginine vasopressin produces vasoconstriction through the Gq/11-phospholipase C-inositol trisphosphate-diacylglycerol signaling cascade, which mobilizes intracellular calcium and activates protein kinase C, leading to myosin light chain phosphorylation and smooth muscle contraction. In septic shock, endogenous vasopressin stores are depleted (the "relative vasopressin deficiency" of prolonged sepsis), and exogenous V1a receptor agonism restores vascular tone through a catecholamine-independent mechanism [15].

Selepressin activates the human V1a receptor with an EC<sub>50</sub> of 2.4 nanomolar in calcium mobilization functional assays, compared to 0.24 nanomolar for native AVP [2]. The approximately 10-fold lower potency relative to AVP at the V1a receptor is offset by the absence of activity at the other three receptor subtypes; the net pharmacological effect at equivasopressor doses is V1a agonism without the V2, V1b, or oxytocin receptor-mediated side effects. In isolated rat mesenteric artery preparations, selepressin produced vasoconstriction with an EC<sub>50</sub> of 3.6 nanomolar (versus 0.8 nanomolar for AVP), and in the rat ear skin blood flow assay the vasoconstrictive ED<sub>50</sub> was 4.0 picomoles per kilogram per minute (versus 3.4 for AVP) [2].

## 4.2 V1a selectivity and absence of V2 receptor activation

The V2 vasopressin receptor (V2R, AVPR2) is expressed predominantly on principal cells of the renal collecting duct and on vascular endothelial cells. V2R activation by AVP produces three effects relevant to septic shock management: insertion of aquaporin-2 water channels into the apical membrane of collecting duct principal cells (producing antidiuresis and free water retention); exocytosis of Weibel-Palade bodies from endothelial cells (releasing von Willebrand factor multimers and P-selectin); and modulation of endothelial permeability through mechanisms that remain incompletely characterized.

Selepressin demonstrates a V1a-to-V2 selectivity ratio of 1:1107, meaning that the V2 receptor is activated only at concentrations approximately 1100-fold higher than those required for V1a activation [2]. At the infusion rates studied in clinical trials (1.7 to 3.5 nanograms per kilogram per minute), plasma concentrations of selepressin are orders of magnitude below the V2 activation threshold. Rehberg et al. (2012) confirmed the functional significance of this selectivity in chronically instrumented sheep: selepressin produced only a 9 plus or minus 2 percent increase in von Willebrand factor antigen-to-hemoglobin ratio (not significantly different from saline controls), compared to a 25 plus or minus 4 percent increase with AVP and a 40 plus or minus 6 percent increase with desmopressin (a selective V2 agonist) [3]. The absence of V2-mediated von Willebrand factor release eliminates a procoagulant stimulus that is particularly hazardous in septic shock patients with concurrent disseminated intravascular coagulation.

## 4.3 Endothelial barrier protection

Barabutis et al. (2020) characterized the mechanism by which V1a receptor activation protects endothelial barrier integrity in human lung microvascular endothelial cells [8]. Selepressin counteracted the barrier-disruptive effects of four endothelial permeability mediators (thrombin, vascular endothelial growth factor, angiotensin-2, and lipopolysaccharide) in a concentration-dependent manner, as measured by transendothelial electrical resistance. The protective mechanism involved activation of the p53 tumor suppressor protein, suppression of the RhoA/myosin light chain 2 inflammatory signaling pathway, and activation of the Rac1 GTPase barrier-protective pathway. The effects were abolished by V1a receptor antagonism or by V1aR silencing with small interfering RNA, confirming that the barrier protection is receptor-mediated and not a nonspecific peptide effect.

The endothelial barrier protection mechanism is clinically significant because capillary leak is a cardinal pathophysiological feature of septic shock, and the resulting interstitial edema contributes to organ dysfunction, prolonged mechanical ventilation, and mortality. The Maybauer et al. (2014) ovine study demonstrated the in vivo translation of this mechanism: selepressin almost completely prevented the pathological fluid accumulation observed in severe ovine sepsis, whereas AVP (which activates both V1a and V2 receptors) produced only partial protection [5].

## 4.4 Absence of V1b and oxytocin receptor activation

The V1b receptor (AVPR1B) is expressed predominantly in the anterior pituitary gland and mediates adrenocorticotrophic hormone release. The oxytocin receptor (OXTR) is expressed on myometrial smooth muscle and on mammary myoepithelial cells and mediates uterine contraction and milk ejection. Selepressin demonstrates V1a-to-V1b and V1a-to-oxytocin selectivity ratios of 1:142 and 1:440, respectively [2], indicating negligible activation of either receptor at vasopressor-relevant concentrations. The absence of V1b activation avoids corticotrophic stimulation, and the absence of oxytocin receptor activation avoids uterotonic effects, both of which are considerations in the obstetric population.

## 5. Pharmacokinetics and Routes of Administration

### 5.1 Absorption and administration

Selepressin is a nonapeptide and is not orally bioavailable owing to proteolytic degradation in the gastrointestinal tract. The compound is administered exclusively by continuous intravenous infusion. In the Phase IIa clinical trial, selepressin was administered as a continuous intravenous infusion at rates of 1.25, 2.5, and 3.75 nanograms per kilogram per minute [9]. In the SEPSIS-ACT trial, starting infusion rates of 1.7, 2.5, and 3.5 nanograms per kilogram per minute were studied, with titration guided by hemodynamic parameters [10].

### 5.2 Distribution

Formal volume of distribution data in humans have not been published in the peer-reviewed literature. The compound is a polar nonapeptide with a molecular weight of 1048 daltons, predicting limited distribution beyond the vascular and extracellular fluid compartments. Plasma protein binding has not been formally characterized in published reports.

### 5.3 Metabolism and elimination

Selepressin is a peptide and is expected to be cleared by tissue peptidases and by renal and hepatic clearance mechanisms common to other nonapeptide vasopressin analogs. The compound was designed to be short-acting with a duration of action comparable to native AVP, as confirmed in rat intravenous bolus studies where the vasopressive effect duration was similar to that of equivasopressor doses of AVP [1]. The short duration of action was a deliberate design feature, enabling rapid titration of the vasopressor effect in the hemodynamically unstable septic shock patient. A quantitative bioanalytical method for determination of selepressin in human plasma at concentrations as low as single-digit picograms per milliliter

was developed using coupled-column liquid chromatography-tandem mass spectrometry [11], reflecting the very low plasma concentrations achieved at therapeutic infusion rates.

## 5.4 Pharmacokinetic-pharmacodynamic relationships

In the Phase IIa trial, the 2.5 nanogram per kilogram per minute infusion rate produced steady-state hemodynamic effects within 2 to 4 hours, with approximately 50 percent and 70 percent of patients maintaining mean arterial pressure above 60 millimeters of mercury without norepinephrine at 12 and 24 hours, respectively [9]. The pharmacodynamic offset after discontinuation of infusion was rapid, consistent with the short-acting peptide design.

## 5.5 Special populations

Formal pharmacokinetic studies in renal impairment, hepatic impairment, or pediatric populations have not been published. Septic shock patients in the clinical trials included patients with acute kidney injury and renal replacement therapy; the peptidase-mediated clearance mechanism predicts that renal impairment would not substantially alter selepressin pharmacokinetics, though formal confirmation is absent. No dose adjustments based on hepatic or renal function were employed in the SEPSIS-ACT trial.

## 6. Preclinical Pharmacology

### 6.1 Canine hemodynamic characterization

Boucheix et al. (2013) performed the first published in vivo hemodynamic comparison of selepressin and AVP in eight anesthetized, instrumented male dogs [7]. Dose-escalating infusions of selepressin (1 to 300 nanograms per kilogram per minute) and AVP (0.3 to 100 nanograms per kilogram per minute) produced comparable increases in mean blood pressure (13 to 18 percent), comparable decreases in aortic blood flow (40 to 45 percent), and comparable decreases in coronary blood flow (16 to 22 percent). The study concluded that selepressin and AVP produced similar hemodynamic profiles and that selepressin bore no relevant coronary ischemic liability beyond what was observed with AVP.

### 6.2 Ovine *Pseudomonas aeruginosa* pneumonia and smoke inhalation

Maybauer et al. (2014) studied selepressin in 45 chronically instrumented sheep with *Pseudomonas aeruginosa* pneumonia combined with smoke inhalation injury [5]. Untreated septic controls accumulated approximately 7 liters of fluid over 24 hours. AVP partially reduced this accumulation. Selepressin almost completely blocked fluid accumulation. When the V2 agonist desmopressin was added to selepressin, fluid accumulation returned to levels similar to AVP, directly demonstrating that V2 receptor activation is responsible for the pathological fluid retention. Both selepressin and AVP restored mean arterial pressure and systemic vascular resistance index when titrated to maintain baseline hemodynamics. The study established the mechanistic basis for the fluid-sparing advantage of V1a selectivity over mixed V1a/V2 agonism.

### 6.3 Ovine fecal peritonitis

He et al. (2016) conducted a randomized study in 46 adult female sheep with fecal peritonitis-induced septic shock [4]. Animals were randomized to selepressin (1 picomole per kilogram per minute), AVP (0.25 picomoles per kilogram per minute), norepinephrine (3 nanomoles per kilogram per minute), or saline control. Two in-

intervention timing protocols were tested: late intervention (initiated when mean arterial pressure fell below 70 millimeters of mercury despite fluid resuscitation) and early intervention (initiated when mean arterial pressure fell 10 percent from baseline). In the early-intervention protocol, selepressin maintained mean arterial pressure and cardiac index better than AVP or norepinephrine. Blood lactate increased more gradually with selepressin. Lung wet-to-dry weight ratios were lower in selepressin-treated animals in both intervention phases. Interleukin-6 and nitrite/nitrate levels were lower in the early-intervention selepressin group. Selepressin-treated animals survived significantly longer than all other groups.

## 6.4 Rabbit endotoxemia

Milano et al. (2020) compared selepressin, AVP, and norepinephrine in a rabbit lipopolysaccharide-induced endotoxemia model with fluid resuscitation [6]. AVP induced a pronounced decrease in mesenteric blood flow, whereas the reduction after selepressin treatment was significantly less. AVP caused pronounced reduction in gastric mucosa perfusion; selepressin showed significantly less reduction in endotoxemic animals. The study concluded that the risk for mesenteric ischemia with selepressin treatment was not inferior to AVP, being less in endotoxemic than in non-endotoxemic animals.

## 6.5 Procoagulant effects

Rehberg et al. (2012) demonstrated in 24 chronically instrumented sheep that selepressin, unlike AVP and desmopressin, does not release von Willebrand factor from endothelial Weibel-Palade bodies [3]. The von Willebrand factor antigen-to-hemoglobin ratio increased by 40 plus or minus 6 percent with desmopressin (V2 agonist), 25 plus or minus 4 percent with AVP (mixed agonist), and only 9 plus or minus 2 percent with selepressin (V1a selective), the last not significantly different from saline controls. This finding has clinical relevance in septic shock patients with disseminated intravascular coagulation, where additional procoagulant stimulation from exogenous vasopressin may exacerbate microvascular thrombosis.

## 6.6 Endothelial barrier protection mechanisms

Barabutis et al. (2020) characterized the molecular mechanism of V1a-receptor-mediated endothelial barrier protection using human lung microvascular endothelial cells [8]. Selepressin counteracted barrier disruption induced by four mechanisti-

cally distinct mediators (thrombin, VEGF, angiopoietin-2, LPS) in a concentration-dependent manner. The signaling mechanism involved activation of the p53 tumor suppressor, suppression of RhoA/MLC2 contractile signaling, and engagement of the Rac1 GTPase pathway that promotes cortical actin stabilization and VE-cadherin junction integrity. V1a receptor antagonism or siRNA-mediated V1aR knock-down abolished the protective effect.

# 7. Clinical Evidence Base

## 7.1 Phase IIa trial

The Phase IIa randomized, double-blind, placebo-controlled trial (NCT01000649, registered September 30, 2009) was conducted by Russell et al. and published in Critical Care in 2017 [9]. The trial enrolled 53 adults with early septic shock requiring vasopressor support after adequate fluid resuscitation. Patients were randomized to selepressin at 1.25 nanograms per kilogram per minute (n equals 10), 2.5 nanograms per kilogram per minute (n equals 19), 3.75 nanograms per kilogram per minute (n equals 2, discontinued), or placebo (n equals 21). Treatment was administered for a maximum of 7 days or until shock resolution.

The 2.5 nanogram per kilogram per minute dose demonstrated superior performance across multiple endpoints. Approximately 50 and 70 percent of patients in this dose group maintained mean arterial pressure above 60 millimeters of mercury without norepinephrine at 12 and 24 hours, respectively, compared to lower rates in the 1.25 nanogram per kilogram per minute and placebo groups. The 7-day cumulative norepinephrine dose was 249 micrograms per kilogram in the 2.5 nanogram per kilogram per minute group versus 761 micrograms per kilogram in the placebo group. Norepinephrine dose at 24 hours was 0.04 versus 0.18 micrograms per kilogram per minute (P less than 0.001). Cumulative net fluid balance was lower from day 5 onward in the 2.5 nanogram per kilogram per minute group (P less than 0.05). Ventilator-free days were significantly greater with the 2.5 nanogram per kilogram per minute dose versus placebo (P less than 0.02). Treatment-emergent adverse events were similar in frequency between selepressin 2.5 nanograms per kilogram per minute and placebo.

The 3.75 nanogram per kilogram per minute dose arm was discontinued after enrollment of only 2 patients owing to possible safety concerns in one patient, and this dose was not advanced further.

## 7.2 SEPSIS-ACT Phase 2b/3 trial

The pivotal SEPSIS-ACT trial (NCT02508649) was an adaptive Phase 2b/3 randomized clinical trial designed by Lewis et al. (2018) and reported by Laterre et al. (2019) in JAMA [10, 13]. The trial received FDA Special Protocol Assessment agreement and enrolled 868 adults with septic shock across 63 hospitals in Belgium, Denmark, France, the Netherlands, and the United States between July 2015 and August 2017, with follow-up completed in May 2018.

The trial design comprised two parts. Part 1 employed Bayesian response-adaptive randomization to evaluate three selepressin dosing regimens (starting infusion rates of 1.7, 2.5, and 3.5 nanograms per kilogram per minute) versus placebo, with prespecified futility stopping rules. Part 2, if triggered, would randomize at least 1000 patients equally to the selected regimen versus placebo. The total planned enrollment of 1800 patients would provide 91 percent power to detect an increase of 1.5 vasopressor- and ventilator-free days with a concurrent 1.5 percent mortality reduction.

Of 868 enrolled patients, 828 received study drug (562 selepressin, 266 placebo). Mean age was 66.3 years; 41.2 percent were female. Median study drug duration was 37.8 hours. The trial was stopped for futility at the completion of Part 1, as no dosing regimen achieved the prespecified Bayesian probability threshold for success.

**Primary endpoint:** Ventilator- and vasopressor-free days within 30 days were 15.0 days with selepressin versus 14.5 days with placebo (difference 0.6 days; 95 percent confidence interval, negative 1.3 to 2.4; P equals 0.30).

**Secondary endpoints:** 90-day mortality was 40.6 percent with selepressin versus 39.4 percent with placebo (difference 1.1 percent; 95 percent confidence interval, negative 6.5 to 8.8 percent; P equals 0.77). Kidney replacement therapy-free days were 18.5 versus 18.2 days (P equals 0.85). ICU-free days were 12.6 versus 12.2 days (P equals 0.41).

**Hemodynamic and fluid-balance endpoints:** Cardiovascular Sequential Organ Failure Assessment score at 24 hours was 3.2 with selepressin versus 3.7 with placebo (difference negative 0.42; 95 percent confidence interval, negative 0.65 to negative 0.19; P less than 0.001). Cardiovascular SOFA score at 48 hours was 2.5 versus 2.9 (difference negative 0.33; P equals 0.003). Hourly fluid balance at 24 hours was 81 milliliters per hour with selepressin versus 107 milliliters per hour with

placebo (difference negative 26 milliliters per hour; 95 percent confidence interval, negative 38 to negative 14; P less than 0.001). Fluid balance at 48 hours did not reach statistical significance.

## 7.3 Interpretation of clinical evidence

The SEPSIS-ACT trial confirmed the preclinical pharmacodynamic signature of selepressin: V1a-selective agonism produces hemodynamic support and fluid sparing relative to standard vasopressor therapy. The failure to translate these pharmacodynamic effects into improvement on patient-centered outcomes (ventilator-free days, mortality) is attributable to several factors discussed in the post-trial literature. First, the trial design added selepressin to ongoing norepinephrine therapy rather than testing selepressin as a first-line vasopressor replacement, potentially limiting the ability to detect a catecholamine-sparing benefit. Second, the trial was stopped before the highest planned dose (5.0 nanograms per kilogram per minute) could be evaluated. Third, the adaptive design with interim futility analysis is conservative by design and may terminate trials with real but modest effect sizes. Fourth, the 24-hour hemodynamic and fluid-balance benefits may require longer exposure or different patient selection to translate into 30-day outcomes. Commentary in the post-trial literature has advocated for future trials focused on early intervention with multimodal vasopressor strategies combining alpha-adrenergic and V1a receptor agonism [16].

## 8. Sourcing and Quality Verification

Selepressin is not commercially available as a pharmaceutical product. It is available from specialized peptide synthesis companies and chemical research suppliers (MedChemExpress, Tocris, Cayman Chemical, custom peptide synthesis houses) as a research-grade peptide. Supply is typically in milligram quantities as the trifluoroacetate or acetate salt, lyophilized. Pricing is characteristic of custom synthetic nonapeptides and is substantially higher per milligram than small-molecule research compounds, typically in the range of \$200 to \$800 per milligram depending on quantity and supplier.

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

- Reversed-phase high-performance liquid chromatography area-percent purity, ideally greater than 95 percent
- Electrospray ionization mass spectrometry confirmation of molecular weight (1048.29 plus or minus 0.5 for the monoisotopic  $[M+H]^+$  ion or the appropriate charge state envelope)
- Amino acid analysis to confirm peptide composition and detect substitution or deletion impurities
- Disulfide bridge confirmation (mass spectrometry of reduced versus oxidized peptide, or Ellman assay for free thiol)
- Residual trifluoroacetic acid content determination by ion chromatography or HPLC (relevant for biological assays where TFA can be cytotoxic)
- Endotoxin testing (Limulus amebocyte lysate assay) for preparations intended for in vivo administration, as bacterial endotoxin contamination of synthetic peptides can confound sepsis research

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The research-grade selepressin market is small, and lot-to-lot variability from custom synthesis is expected; on-receipt analytical confirmation is essential for any investigation where dose-response precision is important.

## 9. Reconstitution and Handling

Selepressin is supplied as a lyophilized powder and requires reconstitution prior to use. For in vitro studies, the compound is typically reconstituted in sterile water, normal saline, or dimethyl sulfoxide to prepare concentrated stock solutions (1 to 10 milligrams per milliliter). Aqueous solutions are preferred for cell-based assays to avoid DMSO interference with cellular responses.

For in vivo research applications, reconstitution in sterile normal saline is standard. The reconstituted solution should be used within 24 hours if prepared with sterile water, or within 14 days if prepared with bacteriostatic water for injection and stored at 2 to 8 degrees Celsius. The compound is a peptide and is susceptible to proteolytic degradation, adsorption to glass and plastic surfaces, and oxidative degradation of the disulfide bridge.

Storage recommendations for the lyophilized powder are negative 20 degrees Celsius, desiccated, protected from light. Under these conditions, stability is expected to exceed 12 months. Repeated freeze-thaw cycles of reconstituted solutions should be avoided; single-use aliquoting is recommended. For continuous intravenous infusion in animal models, the compound is dissolved in normal saline and administered through a syringe pump at flow rates calibrated to deliver the target dose in nanograms or picomoles per kilogram per minute, consistent with the dosing paradigms used in the clinical trials.

Investigators should be aware that the trifluoroacetate counterion present in HPLC-purified peptides contributes to the apparent molecular weight and can affect molarity calculations. For precise dosing, the peptide content (net peptide, excluding counterion and residual moisture) should be determined by amino acid analysis and used for concentration calculations rather than the total weighed mass.

## 10. Stack Interactions and Combinations

Selepressin interacts with several drug classes through its V1a-receptor-mediated vasoconstrictive mechanism and through pharmacodynamic interactions in the hemodynamic management of shock states. Investigators conducting research with selepressin, especially in combination with other vasoactive agents, should consider:

**Norepinephrine and other catecholamine vasopressors:** Selepressin was studied in clinical trials as an adjunct to ongoing norepinephrine therapy. The combination produces additive vasopressor effects through complementary mechanisms (alpha-1 adrenergic plus V1a vasopressin receptor-mediated vasoconstriction). The Phase IIa trial demonstrated that selepressin at 2.5 nanograms per kilogram per minute substantially reduced norepinephrine requirements [9]. Concurrent use is the intended clinical application and is well characterized.

**Arginine vasopressin:** Concurrent administration of selepressin and AVP would produce additive V1a agonism with AVP contributing additional V2, V1b, and oxytocin receptor activation, eliminating the V1a selectivity advantage of selepressin. The combination is pharmacologically redundant and is not recommended.

**Terlipressin:** Terlipressin is a long-acting vasopressin analog with substantial V2 activity. Concurrent use with selepressin would introduce V2-mediated effects that selepressin is designed to avoid. The combination has not been studied and is not pharmacologically rational.

**Angiotensin II:** Angiotensin II (Giapreza, approved by the FDA in 2017 for refractory vasodilatory shock) acts through the angiotensin II type 1 receptor, a mechanism independent of and complementary to V1a agonism. The combination of V1a agonism and angiotensin II receptor agonism has not been formally studied but represents a mechanistically rational multimodal vasopressor strategy. Meta-analyses have evaluated both agents as non-adrenergic vasopressors in septic shock [17].

**Corticosteroids:** Hydrocortisone is commonly administered in refractory septic shock. Corticosteroids upregulate vasopressin V1a receptor expression and sensitize the vasculature to vasopressor effects. The interaction is potentially synergistic and is clinically relevant in the context of the Surviving Sepsis Campaign guidelines that recommend corticosteroid adjunction.

**Inotropes (dobutamine, milrinone):** Septic shock with myocardial depression may require inotropic support in addition to vasopressor therapy. Selepressin does not have positive inotropic activity; concurrent inotrope use is complementary and has not been shown to produce adverse pharmacodynamic interactions.

**Fluids and volume resuscitation:** The fluid-sparing effect of selepressin (reduced hourly fluid balance relative to placebo) is one of the pharmacodynamic advantages observed in clinical trials. Investigators should monitor fluid balance carefully when combining selepressin with aggressive volume resuscitation protocols, as the V1a-selective mechanism may alter the fluid-response relationship.

# 11. Adverse Events and Safety Signal

## 11.1 Preclinical safety

In the Boucheix et al. (2013) canine hemodynamic study, selepressin produced dose-dependent vasoconstriction with associated reductions in aortic and coronary blood flow comparable to equipressor doses of AVP [7]. No coronary ischemic events were observed. In ovine sepsis models, selepressin was well tolerated at the studied doses; no treatment-emergent safety signals distinct from the underlying septic process were reported [4, 5].

## 11.2 Phase IIa adverse events

In the Russell et al. (2017) Phase IIa trial, treatment-emergent adverse events were similar in frequency between selepressin 2.5 nanograms per kilogram per minute and placebo [9]. The 3.75 nanogram per kilogram per minute dose arm was discontinued after enrollment of only 2 patients owing to possible safety concerns in one patient, suggesting that higher doses may approach the therapeutic ceiling for the vasoconstrictive effect.

## 11.3 SEPSIS-ACT adverse events

In the SEPSIS-ACT trial (Laterre et al. 2019), the following adverse event rates were reported [10]:

- Cardiac arrhythmias: 27.9 percent with selepressin versus 25.2 percent with placebo
- Cardiac ischemia: 6.6 percent versus 5.6 percent
- Mesenteric ischemia: 3.2 percent versus 2.6 percent
- Peripheral ischemia: 2.3 percent versus 2.3 percent

None of these differences was statistically significant. The adverse event profile was broadly similar between selepressin and placebo groups, consistent with a favorable safety profile at the studied doses. The rates of ischemic events (mesenteric,

peripheral, cardiac) are characteristic of the underlying septic shock population and of concurrent catecholamine vasopressor therapy rather than of selepressin-specific toxicity.

## 11.4 Mesenteric ischemia considerations

Jozwiak et al. (2022) reported a worldwide pharmacovigilance analysis of vasopressors and risk of acute mesenteric ischemia [18]. Selepressin showed no significant association with acute mesenteric ischemia, unlike some other vasopressors. The Milano et al. (2020) preclinical study in rabbits demonstrated that selepressin produced less reduction in mesenteric blood flow than AVP [6], supporting a potentially more favorable splanchnic perfusion profile.

## 11.5 Digital ischemia

Commentary by Jozwiak (2022) noted that selepressin has been associated with digital ischemia in some reports, which has contributed to cautious clinical adoption [19]. The frequency and clinical significance of this finding relative to other vasopressors in the septic shock setting remain incompletely characterized.

## 11.6 General safety considerations

Selepressin is a potent vasoconstrictor and carries the class risks of all vasopressor agents: excessive vasoconstriction can produce end-organ ischemia (digital, mesenteric, myocardial, renal). Dose titration guided by hemodynamic monitoring is essential. The short-acting pharmacokinetic profile of selepressin is a safety advantage relative to long-acting vasopressin analogs (terlipressin), as excessive vasoconstriction can be rapidly reversed by discontinuation of the infusion.

## 12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five vasopressor or vasopressin-pathway agents against selepressin, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile (clinical or preclinical), and overall validation. The five comparators were selected as the principal vasopressor alternatives evaluated or available for the management of vasodilatory shock, with priority on agents that share the non-catecholamine vasopressor mechanism or the vasopressin receptor pharmacology space.

### 12.1 Arginine vasopressin (AVP)

**Mechanism:** Endogenous nonapeptide hormone acting as a full agonist at V1a, V1b, V2, and oxytocin receptors. The V1a-mediated vasoconstriction is the basis for its use as a vasopressor in septic shock.

**Clinical evidence:** The VASST trial (Russell et al. 2008, NEJM) randomized 778 patients with septic shock to low-dose AVP (0.03 units per minute) plus norepinephrine versus norepinephrine alone [12]. AVP did not reduce 28-day mortality in the overall population (35.4 versus 39.3 percent, P equals 0.26) but showed a significant mortality reduction in the less-severe septic shock subgroup. The VANISH trial (Gordon et al. 2016, JAMA) similarly found no overall mortality benefit but demonstrated reduced renal replacement therapy requirements with early vasopressin [20]. AVP is included in the Surviving Sepsis Campaign guidelines as a second-line vasopressor.

**Novelty:** Low. AVP is an endogenous hormone with decades of clinical use. Its vasopressin receptor pharmacology is well characterized but nonselective.

**Effect size:** Modest. VASST showed a 3.9 percent absolute mortality reduction in the overall population (not significant) and a significant subgroup effect. VANISH showed renal-sparing benefit.

**Promising potential:** Established. AVP is an approved pharmaceutical with widespread clinical use. It is the current standard of care for non-catecholamine vasopressor support in septic shock.

**Side-effect profile:** V2-mediated fluid retention, von Willebrand factor release, and potential exacerbation of coagulopathy. Digital and mesenteric ischemia at higher doses. Hyponatremia from V2-mediated free water retention.

**Overall validation:** High. Multiple large randomized controlled trials, guideline recommendations, and decades of clinical experience.

**Comparison to selepressin:** Selepressin was designed to replicate the V1a-mediated benefits of AVP while eliminating V2-mediated harms. Preclinical evidence supports this pharmacological rationale. The SEPSIS-ACT trial failed to demonstrate superior patient-centered outcomes relative to placebo (with ongoing norepinephrine), and no head-to-head comparison of selepressin versus AVP has been conducted in a randomized clinical trial.

## 12.2 Terlipressin

**Mechanism:** Synthetic vasopressin analog (triglycyl-lysine vasopressin) with preferential V1a activity but substantial V2 agonism. It is a prodrug converted to lysine vasopressin by tissue endopeptidases, producing a longer duration of action (4 to 6 hours) than AVP.

**Clinical evidence:** Multiple randomized trials in septic shock and in hepatorenal syndrome. The TERLIVAP trial (Morelli et al. 2009) compared terlipressin plus norepinephrine to AVP plus norepinephrine in 45 patients with septic shock and found comparable hemodynamic effects but higher adverse event rates with terlipressin [21]. The compound is approved in some jurisdictions for hepatorenal syndrome (CONFIRM trial, 2021) but not for septic shock.

**Novelty:** Low. Terlipressin is a well-characterized vasopressin prodrug with a long clinical history in variceal bleeding and hepatorenal syndrome.

**Effect size:** Comparable hemodynamic support to AVP in septic shock. Strong evidence for hepatorenal syndrome reversal.

**Promising potential:** Moderate for septic shock (not the primary indication). High for hepatorenal syndrome (approved indication in some jurisdictions).

**Side-effect profile:** V2-mediated fluid retention, digital ischemia (reported at higher rates than AVP in some studies), mesenteric ischemia. The long duration of action limits titrability and is a disadvantage in hemodynamically labile patients.

**Overall validation:** Moderate for septic shock. High for hepatorenal syndrome and variceal bleeding.

**Comparison to selepressin:** Selepressin has greater V1a selectivity (selectivity ratio 1:1107 for V1a over V2, compared to terlipressin which retains substantial V2 activity). Selepressin has a shorter duration of action enabling more precise hemodynamic titration. Terlipressin has broader clinical validation and approved indications. Neither agent has demonstrated mortality benefit in septic shock in a large randomized trial.

## 12.3 Angiotensin II

**Mechanism:** Endogenous octapeptide hormone acting at the angiotensin II type 1 receptor (AT1R) to produce vasoconstriction through a mechanism independent of both adrenergic and vasopressin pathways.

**Clinical evidence:** The ATHOS-3 trial (Khanna et al. 2017, NEJM) randomized 344 patients with refractory vasodilatory shock to angiotensin II or placebo [22]. Angiotensin II significantly improved mean arterial pressure response at 3 hours (69.9 versus 23.4 percent, P less than 0.001) and showed a trend toward reduced mortality at day 28. The compound was approved by the FDA in 2017 (Giapreza) for refractory vasodilatory shock.

**Novelty:** Moderate. Angiotensin II was known as an endogenous vasoconstrictor for decades but was only recently developed and approved as a pharmaceutical vasopressor.

**Effect size:** Large hemodynamic effect (blood pressure response). Mortality trend but not significant in the overall ATHOS-3 population.

**Promising potential:** High. Approved by the FDA. Active use in refractory vasodilatory shock. Post-marketing studies ongoing.

**Side-effect profile:** Thrombotic events (deep vein thrombosis, reported at higher rates than placebo in ATHOS-3). Potential for excessive vasoconstriction. Interaction with renin-angiotensin system modulators.

**Overall validation:** Moderate to high. FDA-approved based on a single pivotal trial. Growing real-world evidence and guideline incorporation.

**Comparison to selepressin:** Angiotensin II acts through a completely different receptor mechanism (AT1R versus V1aR). The two agents are mechanistically complementary and could theoretically be combined in a multimodal vasopressor strategy. Angiotensin II succeeded in FDA registration where selepressin did not, though the trial designs and patient populations differed substantially. Angiotensin II is available as a licensed pharmaceutical; selepressin is not.

## 12.4 Methylene blue

**Mechanism:** Inhibitor of guanylate cyclase and nitric oxide synthase. Methylene blue reduces pathological nitric oxide-mediated vasodilation in refractory vasodilatory shock by blocking the nitric oxide-cyclic GMP-protein kinase G vasodilatory pathway.

**Clinical evidence:** Multiple small randomized trials and case series in cardiac surgery-associated vasoplegia and refractory septic shock. A meta-analysis by Kotani et al. (2024) included methylene blue among non-adrenergic vasopressors for vasodilatory shock [17]. Evidence is heterogeneous and principally from small single-center studies. The compound is not approved for vasopressor indications.

**Novelty:** Moderate. The application of methylene blue as a vasopressor is a repositioning of a century-old dye and redox agent.

**Effect size:** Variable. Case series and small trials report dramatic hemodynamic rescue in selected patients with refractory vasoplegia. Effect sizes in formal randomized trials are inconsistent.

**Promising potential:** Low to moderate. No pivotal registration trial. Continued use as a rescue vasopressor in refractory cases.

**Side-effect profile:** Methemoglobinemia at high doses. Serotonin toxicity risk in combination with serotonergic agents. Interference with pulse oximetry readings. Blue discoloration of skin and urine.

**Overall validation:** Low. Small, heterogeneous evidence base. No regulatory approval for vasopressor indications.

**Comparison to selepressin:** Methylene blue acts through a fundamentally different mechanism (nitric oxide pathway inhibition versus V1a receptor agonism). The two approaches address different pathophysiological components of vasodilatory shock. Selepressin has a larger and more rigorous clinical evidence base, including the 868-patient SEPSIS-ACT trial, whereas methylene blue evidence is principally from small studies and case series.

## 12.5 Hydroxocobalamin

**Mechanism:** Vitamin B12 analog that scavenges nitric oxide and hydrogen sulfide, producing vasoconstriction through reduction of pathological vasodilatory mediators. Also inhibits soluble guanylate cyclase.

**Clinical evidence:** Case series and small studies in refractory vasodilatory shock after cardiac surgery and in septic shock. Included in the Kotani et al. (2024) meta-analysis of non-adrenergic vasopressors [17]. A small randomized trial in cardiac surgery vasoplegia reported hemodynamic improvement. The compound is approved for cyanide poisoning (Cyanokit) but not for vasopressor indications.

**Novelty:** Moderate. Repositioning of a vitamin B12 analog for vasopressor effects is a recent development in critical care pharmacology.

**Effect size:** Variable. Reports of dramatic hemodynamic rescue in individual cases and small series. Formal effect size quantification in randomized trials is limited.

**Promising potential:** Low to moderate. No pivotal registration trial for vasopressor indications. Continued use as a rescue agent in selected centers.

**Side-effect profile:** Red discoloration of skin and urine (interferes with laboratory assays). Hypertension at high doses. Generally well tolerated at doses used for vasopressor rescue.

**Overall validation:** Low. Small evidence base. No regulatory approval for vasopressor indications.

**Comparison to selepressin:** Hydroxocobalamin acts through nitric oxide and hydrogen sulfide scavenging rather than receptor-mediated vasoconstriction. The mechanism is complementary to V1a agonism. Selepressin has a substantially

more developed clinical evidence base, including a Phase 2b/3 trial, whereas hydroxocobalamin evidence for vasopressor indications is principally observational.

## 12.6 Comparator summary

The five comparators occupy distinct positions in the vasopressor pharmacology space. **Arginine vasopressin** is the established non-catecholamine vasopressor with the largest clinical evidence base and guideline support, but its nonselective receptor activation produces V2-mediated harms that selepressin was designed to avoid. **Terlipressin** is a long-acting vasopressin prodrug with proven efficacy in hepatorenal syndrome but limited evidence and less favorable titrability in septic shock. **Angiotensin II** is the most recently approved non-catecholamine vasopressor, acting through a completely independent receptor pathway, and represents the most successful recent addition to the vasopressor armamentarium. **Methylene blue** and **hydroxocobalamin** are mechanistically distinct rescue vasopressors with small, heterogeneous evidence bases.

Selepressin occupies a unique pharmacological position as the only clinically tested selective V1a receptor agonist. Its preclinical pharmacology is compelling: superior hemodynamic support, fluid sparing, vascular leak prevention, and survival benefit relative to AVP and norepinephrine in multiple sepsis models. The clinical translation, however, failed to demonstrate patient-centered outcome benefit in the SEPSIS-ACT trial, despite confirming the hemodynamic and fluid-balance pharmacodynamic advantages. The compound's development trajectory illustrates a recurring challenge in critical care pharmacology: pharmacodynamic signals that are robust in preclinical models and in short-term clinical endpoints may not translate into improvements in composite outcomes (ventilator-free days, 30-day mortality) in heterogeneous critically ill populations.

The principal lessons from the selepressin development program for the broader vasopressor research field are: first, that V1a selectivity confers measurable fluid-sparing and hemodynamic benefits relative to nonselective vasopressin receptor agonism; second, that these benefits alone may be insufficient to alter patient-centered outcomes in the current standard-of-care context; and third, that future development of V1a-selective agents may require different trial designs (early intervention, first-line vasopressor replacement rather than adjunction, enrichment for

patients with high fluid balance or V2-mediated harms) or combination strategies (concurrent V1a agonism and alpha-adrenergic or angiotensin-mediated vasoconstriction) to demonstrate clinical benefit.

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