

## RESEARCH MONOGRAPH . COMPOUND PROFILE

# Carbetocin

*A 1-deamino-1-monocarba analog of oxytocin developed by Ferring Pharmaceuticals as a heat-stable uterotonic for the prevention of postpartum hemorrhage, distinguished from native oxytocin by enzymatic resistance, prolonged duration of action, functional selectivity at the Gq signaling pathway, and investigational application in Prader-Willi syndrome hyperphagia.*

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## ABSTRACT

Carbetocin (1-deamino-1-monocarba-(2-O-methyltyrosine)-oxytocin; CAS 37025-55-1; molecular formula C<sub>45</sub>H<sub>69</sub>N<sub>11</sub>O<sub>12</sub>S; molecular weight 988.16) is a synthetic long-acting analog of the neurohypophysial peptide oxytocin, developed for the prevention of uterine atony and postpartum hemorrhage following cesarean and vaginal delivery. The compound incorporates two critical structural modifications relative to native oxytocin: replacement of the disulfide bridge with a thioether (monocarba) linkage that confers resistance to disulfide reductases, and deamination of the N-terminal cysteine residue that eliminates aminopeptidase-mediated degradation. These modifications extend the plasma elimination half-life from approximately 3 to 4 minutes (oxytocin) to approximately 40 to 85 minutes (carbetocin), producing sustained uterotonic activity from a single 100 microgram intravenous or intramuscular injection [1, 2]. Carbetocin acts as a selective agonist at the oxytocin receptor (OXTR), a class A G protein-coupled receptor expressed on myometrial smooth muscle, myoepithelial cells of the mammary gland, and neuronal populations in the hypothalamus, amygdala, and brainstem. Molecular pharmacology studies have characterized carbetocin as a functionally selective (biased) Gq agonist: it activates the Gq/phospholipase C/inositol trisphosphate signaling cascade with partial agonist efficacy while inducing receptor internalization through a beta-arrestin-independent pathway that prevents receptor recycling to the plasma membrane [3]. This functional selectivity profile distinguishes carbetocin from native oxytocin (which recruits both Gq and beta-arrestin pathways) and from vasopressin V1a/V1b receptors at which carbetocin shows

negligible agonist activity. The compound was first approved in 1997 (Duratocin, Pabal; Ferring Pharmaceuticals) for prevention of uterine atony following cesarean delivery and is now registered in more than 80 countries. The World Health Organization CHAMPION trial (Widmer et al. 2018), a 29,645-patient multinational randomized noninferiority study, demonstrated that a heat-stable formulation of carbetocin (100 microgram intramuscular) was noninferior to oxytocin (10 IU intramuscular) for prevention of postpartum hemorrhage after vaginal birth, establishing the compound as a viable alternative in settings where cold-chain storage is unavailable [4]. A second clinical development program, advanced by Acadia Pharmaceuticals, has evaluated intranasal carbetocin (3.2 to 9.6 mg three times daily) for the treatment of hyperphagia, anxiousness, and distress behaviors in Prader-Willi syndrome (PWS); the CARE-PWS Phase 3 trial (Kimonis et al. 2023) reported clinically meaningful improvements in hyperphagia at the 3.2 mg dose in 130 participants aged 7 to 18 years [5, 6]. Pharmacokinetics after intravenous administration show biphasic elimination with a terminal half-life of approximately 33 minutes; intramuscular administration produces a terminal half-life of approximately 55 minutes with bioavailability exceeding 80 percent [7]. The compound is well tolerated at registered doses; principal adverse events are nausea, vomiting, abdominal pain, flushing, headache, and transient hypotension, with a safety profile comparable to or more favorable than standard-dose oxytocin in pooled meta-analytic data [8, 9]. This monograph reviews the chemistry, synthesis, and structural modifications of carbetocin; the biased receptor pharmacology at the oxytocin receptor; comprehensive human pharmacokinetics; preclinical uterotonic and neurobehavioral pharmacology; the clinical evidence base across

postpartum hemorrhage prevention and Prader-Willi syndrome indications; sourcing and quality verification considerations for research applications; reconstitution and handling; stack-interaction implications; adverse-event signal; and a comparative assessment of five alternative uterotonics and oxytocin-system compounds against carbetocin on five competency standards.

# 1. Compound Identification

## 1.1 Names, synonyms, and registry identifiers

**International Nonproprietary Name:** Carbetocin.

**Marketed names:** Duratocin (Ferring Pharmaceuticals; Canada, multiple jurisdictions), Pabal (Ferring; European Union, United Kingdom, Australia, New Zealand), Lonactene (generic markets).

**Development codes:** SDZ 215-811 (Sandoz/Novartis early development), RWJ-22164 (historical), Carbetocin TS (heat-stable formulation designation for the WHO CHAMPION program).

**Chemical Abstracts Service registry number:** 37025-55-1 (free base). The acetate salt is registered under CAS 1631754-28-3. The free base is the pharmacopoeial and research-grade form.

**International Union of Pure and Applied Chemistry name:** 1-butanoic acid-2-(O-methyl-L-tyrosine)-1-carboxytocin. The systematic peptide designation is [1-deamino-1-monocarba-2-O-methyltyrosine]-oxytocin.

**Amino acid sequence:** Butyryl-Tyr(OMe)-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH<sub>2</sub>, with a thioether bond between the butyryl moiety at position 1 and the cysteine sulfur at position 6, forming the characteristic macrocyclic ring [10].

## 1.2 Structural class and chemistry

Carbetocin is a cyclic nonapeptide analog belonging to the neurohypophysial hormone family. It retains the 20-membered ring structure of oxytocin but incorporates two stabilizing modifications: the disulfide bridge (Cys1-Cys6) is replaced by a thioether (carbon-sulfur) linkage formed between a deaminated butyric acid residue at position 1 and the cysteine thiol at position 6, and the tyrosine at position 2 carries an O-methyl ether modification [10, 11].

**Molecular formula:** C<sub>45</sub>H<sub>69</sub>N<sub>11</sub>O<sub>12</sub>S (free base).

**Exact mass:** 987.49 g/mol (free base, monoisotopic).

**Molecular weight:** 988.16 g/mol (free base).

**Physical properties:** White to off-white amorphous or lyophilized powder. Freely soluble in water, soluble in dilute acetic acid and aqueous buffers at pH 3 to 7, sparingly soluble in organic solvents. Hygroscopic; should be stored in tightly closed containers. Melting point approximately 140 to 160 degrees Celsius with decomposition.

**Stereochemistry:** All amino acid residues retain the L-configuration of native oxytocin. The compound is supplied as a single stereoisomer. Investigators acquiring research-grade carbetocin should confirm peptide identity by mass spectrometry and purity by reversed-phase high-performance liquid chromatography.

## 1.3 Synthesis

The synthesis of carbetocin proceeds by solid-phase or solution-phase peptide synthesis methodologies. The critical synthetic challenge is formation of the thioether macrocycle: the N-terminal butyryl moiety bearing a gamma-halide or gamma-activated leaving group is cyclized with the cysteine-6 thiol under mildly basic conditions (cesium carbonate or diisopropylethylamine in dimethylformamide) to form the carbon-sulfur bond that replaces the native disulfide [10, 12]. The O-methyltyrosine at position 2 is incorporated as a protected building block (Fmoc-Tyr(OMe)-OH for solid-phase synthesis). The linear precursor peptide is assembled on Rink amide resin (or equivalent C-terminal amide-generating support), cleaved with trifluoroacetic acid cocktails, and cyclized in solution. Purification is by preparative reversed-phase HPLC; the product is characterized by analytical HPLC (greater than 95 percent purity by area), electrospray ionization mass spectrometry (expected  $[M+H]^+$  989.49), and amino acid analysis. Industrial synthesis for pharmaceutical-grade material achieves greater than 98 percent purity with validated control of des-Gly, deamidation (Asn to Asp), and oxidation (Met-sulfoxide) impurities. The heat-stable formulation developed for the WHO CHAMPION trial consists of carbetocin at 0.1 mg/mL in sodium succinate buffer at pH 5.45 with mannitol as a tonicity agent and L-methionine as an antioxidant [13].

## 2. Abstract

Carbetocin is a synthetic long-acting oxytocin receptor agonist distinguished from native oxytocin by a thioether macrocycle that confers enzymatic resistance, an O-methyltyrosine modification that enhances receptor affinity, and a functional selectivity profile characterized by preferential Gq pathway activation without beta-arrestin recruitment [3]. These modifications produce a compound with approximately 10- to 20-fold longer duration of uterotonic action compared to oxytocin, enabling single-dose prophylaxis of postpartum hemorrhage from a single 100 microgram injection administered after delivery of the anterior shoulder or after cesarean delivery of the infant [1, 4].

The principal registered indication is prevention of uterine atony and postpartum hemorrhage following cesarean section (approved in more than 80 countries since 1997) and following vaginal delivery (WHO Essential Medicines List inclusion 2019, based on the CHAMPION noninferiority trial). The heat-stable formulation represents a significant advance for resource-limited settings: standard oxytocin requires cold-chain storage (2 to 8 degrees Celsius) and degrades rapidly at ambient temperatures in tropical climates, whereas heat-stable carbetocin maintains greater than 95 percent potency for 36 months at 30 degrees Celsius and 75 percent relative humidity [13].

A second clinical program has evaluated intranasal carbetocin for the treatment of behavioral symptoms in Prader-Willi syndrome, a genetic disorder caused by loss of paternal chromosome 15q11-q13 expression and characterized by severe hyperphagia, obesity, behavioral disturbances, and hypothalamic oxytocin system dysfunction [5, 6]. The Phase 2 trial (Dyken et al. 2018) in 37 participants and the CARE-PWS Phase 3 trial (Kimonis et al. 2023) in 130 participants demonstrated dose-dependent reductions in hyperphagia scores and improvements in anxiousness and distress behaviors. The intranasal route delivers carbetocin to central nervous system oxytocin receptor populations via the olfactory and trigeminal nerve pathways, bypassing the blood-brain barrier limitation that restricts peripheral oxytocin administration from achieving central effects at clinical doses [14].

The compound is well tolerated across both the injectable uterotonic and intranasal neurobehavioral applications. Principal adverse events are nausea, vomiting, abdominal pain, flushing, and headache at frequencies of 10 to 40 percent following uterotonic doses; the profile is comparable to standard oxytocin with a lower incidence of gastrointestinal effects compared to the oxytocin-plus-ergometrine combination [8, 9]. Cardiovascular effects (transient hypotension, tachycardia) occur at rates indistinguishable from oxytocin in randomized comparative data.

This monograph documents the complete pharmacology, pharmacokinetics, clinical evidence base, and research-application considerations for carbetocin across its registered uterotonic indication and its investigational neurobehavioral applications.

## 3. Discovery and Development History

### 3.1 Origin and structural design

Carbetocin was first synthesized at the Institute of Organic Chemistry and Biochemistry of the Czechoslovak Academy of Sciences in Prague in the early 1970s as part of a systematic structure-activity program on oxytocin analogs with enhanced metabolic stability [10, 12]. The design rationale addressed the two principal metabolic vulnerabilities of native oxytocin: (a) aminopeptidase-mediated cleavage of the N-terminal half-cystine, which accounts for the majority of peripheral oxytocin degradation and limits the plasma half-life to 3 to 4 minutes; and (b) disulfide bond reduction by hepatic and placental glutathione reductases, which opens the macrocyclic ring and eliminates receptor binding. The 1-deamino modification removes the free alpha-amino group required for aminopeptidase recognition. The 1-monocarba modification replaces the reducible S-S bond with an irreducible C-S thioether. The O-methylation of tyrosine-2 was incorporated to modulate receptor binding kinetics and selectivity. The combined modifications produced a compound with the uterotonic potency of oxytocin but approximately 10- to 20-fold longer duration of action in vivo [11].

### 3.2 Veterinary development

Early development focused on veterinary obstetric applications. US Patent 4,237,119 (filed 1979, granted 1980) by inventors at the Czech Academy of Sciences covered the use of desamino-carba oxytocin analogs for induction of labor and milk let-down in equines and bovines. Carbetocin was commercialized for veterinary use in dairy cattle and swine for prevention of mastitis-metritis-agalactia syndrome and for induction of parturition [15].

### 3.3 Human clinical development

Ferring Pharmaceuticals acquired the human development rights and advanced carbetocin through human pharmacokinetic studies in the late 1980s and early 1990s, followed by Phase 2 and Phase 3 clinical trials for prevention of postpartum hemorrhage following cesarean delivery. The pivotal registration trials compared

single-dose intravenous carbetocin 100 microgram to standard oxytocin infusion protocols and demonstrated noninferior uterotonic efficacy with single-dose convenience [1, 2]. First approval was granted in 1997 in multiple jurisdictions; the compound was registered as Duratocin (Canada, Latin America) and Pabal (European Union, United Kingdom, Australia, New Zealand).

### 3.4 Heat-stable formulation and WHO CHAMPION trial

Recognizing that oxytocin's cold-chain requirement represented a critical barrier to effective postpartum hemorrhage prevention in low- and middle-income countries (where approximately 99 percent of the global maternal mortality burden occurs), Ferring and the WHO collaborated on a heat-stable carbetocin formulation. Malm et al. (2018) published the development and accelerated stability data: the formulation at pH 5.45 in succinate buffer with mannitol and methionine maintained greater than 95 percent peptide purity for 36 months at 30 degrees Celsius [13]. The WHO CHAMPION trial (Carbetocin Haemorrhage Prevention trial; Widmer et al. 2018), published in the New England Journal of Medicine, enrolled 29,645 women in a randomized double-blind noninferiority trial at 23 hospitals across 10 countries (Argentina, Egypt, India, Kenya, Nigeria, Singapore, South Africa, Thailand, Uganda, United Kingdom). Intramuscular heat-stable carbetocin 100 microgram was noninferior to intramuscular oxytocin 10 IU for the primary composite outcome of blood loss of at least 500 mL or use of additional uterotonic agents (14.5 percent versus 14.4 percent; relative risk 1.01, 95 percent confidence interval 0.95 to 1.06) [4]. Based on this trial, carbetocin was included on the WHO Model List of Essential Medicines in 2019 and the WHO issued recommendations for its use as an alternative to oxytocin in the prevention of postpartum hemorrhage.

### 3.5 Prader-Willi syndrome development

Acadia Pharmaceuticals (and previously Levo Therapeutics) advanced intranasal carbetocin for Prader-Willi syndrome based on the hypothesis that hypothalamic oxytocin neuron deficiency underlies the hyperphagia and behavioral disturbances of PWS. The Phase 2 proof-of-concept trial (Dyken et al. 2018) randomized 37 participants aged 10 to 18 to intranasal carbetocin or placebo for 14 days and reported significant reductions in hyperphagia scores [5]. The CARE-PWS Phase 3 trial (Kimonis et al. 2023) enrolled 130 participants aged 7 to 18, randomized to 9.6 mg, 3.2 mg, or placebo three times daily for 8 weeks. The 3.2 mg dose produced clinically meaningful improvements in hyperphagia and anxiousness/distress [6].

Despite positive signals on multiple endpoints, the overall regulatory outcome has been mixed, with the FDA not approving the compound for this indication as of the most recent monograph revision.

## 4. Mechanism of Action

### 4.1 Oxytocin receptor pharmacology

The oxytocin receptor (OXTR) is a class A rhodopsin-like G protein-coupled receptor with 389 amino acid residues, coupled primarily to the heterotrimeric Gq/11 protein. Upon agonist binding, OXTR activates phospholipase C-beta, which hydrolyzes phosphatidylinositol 4,5-bisphosphate to generate inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 mobilizes intracellular calcium from sarcoplasmic reticulum stores; the resulting calcium transient activates myosin light chain kinase and drives actin-myosin cross-bridge cycling in myometrial smooth muscle [16]. This is the molecular basis of uterine contraction.

Carbetocin binds the OXTR orthosteric site with affinity comparable to native oxytocin but with distinct binding kinetics. The thioether macrocycle and O-methyltyrosine modification produce slower dissociation from the receptor, contributing to the prolonged pharmacodynamic effect [3, 11].

### 4.2 Functional selectivity (biased agonism)

The Passoni et al. (2016) characterization of carbetocin at the OXTR represents the most detailed molecular pharmacology study of the compound [3]. Key findings include:

(a) Carbetocin is a partial agonist at the OXTR/Gq coupling, with intrinsic activity approximately 50 to 70 percent of oxytocin maximum in IP3 accumulation assays.

(b) Carbetocin does not recruit beta-arrestin-1 or beta-arrestin-2 to the OXTR at concentrations up to 10 micromolar, in contrast to oxytocin which robustly recruits both beta-arrestins.

(c) Despite the absence of beta-arrestin recruitment, carbetocin induces efficient OXTR internalization through a beta-arrestin-independent, dynamin-dependent pathway.

(d) Following carbetocin-induced internalization, the OXTR does not recycle to the plasma membrane but remains sequestered in intracellular compartments. This contrasts with oxytocin-induced internalization, after which the receptor recycles efficiently.

The functional consequence of this biased signaling profile is that carbetocin produces sustained Gq-mediated uterotonic activity (from the slow dissociation and the Gq partial agonism) followed by prolonged receptor downregulation (from the non-recycling internalization). The net effect is a longer duration of uterine contraction from a single dose compared to oxytocin, which activates and then rapidly recycles the receptor [3].

## 4.3 Receptor selectivity

Carbetocin shows negligible agonist activity at the vasopressin V1a, V1b, and V2 receptors at concentrations up to 1 micromolar. At the V1a receptor, carbetocin has been reported to act as a weak antagonist, blocking vasopressin-induced calcium mobilization without producing intrinsic activity [3, 17]. This selectivity profile distinguishes carbetocin from native oxytocin, which shows meaningful cross-reactivity at the V1a and V2 receptors (the basis for oxytocin's antidiuretic effect at high doses). The absence of vasopressin receptor agonism is clinically relevant: it eliminates the water retention and hyponatremia risk associated with prolonged high-dose oxytocin infusions.

## 4.4 Central nervous system mechanisms

In the context of the Prader-Willi syndrome application, intranasal carbetocin is hypothesized to activate central oxytocin receptors in the hypothalamus (paraventricular and supraoptic nuclei), amygdala, and nucleus accumbens. These populations regulate appetite, social behavior, anxiety, and reward processing. The intranasal route allows the peptide to bypass the blood-brain barrier through transport along olfactory nerve axons and trigeminal nerve branches, achieving cerebrospinal fluid concentrations sufficient for central receptor engagement without the need for systemic doses that would produce excessive peripheral uterotonic effects [14]. The molecular mechanism in PWS is proposed to compensate for the documented reduction in oxytocin-producing neurons and reduced peripheral oxytocin levels observed in PWS patients [5].

## 4.5 Myometrial contractility mechanism

At the myometrial level, the IP<sub>3</sub>-mediated calcium release produced by carbetocin-induced G<sub>q</sub> activation drives rhythmic uterine contractions. The calcium transient activates calmodulin, which binds and activates myosin light chain kinase (MLCK). MLCK phosphorylates the regulatory light chain of myosin II, enabling actin-myosin cross-bridge formation and contraction. Simultaneously, DAG activates protein kinase C, which modulates calcium sensitivity and gap junction coupling between myometrial cells, promoting coordinated uterine contraction [16]. Carbetocin's partial agonist character at G<sub>q</sub> means that the magnitude of individual contractions may be somewhat lower than oxytocin's full agonist response, but the sustained duration of effect (from slow receptor dissociation and receptor sequestration) produces a net uterotonic effect that is clinically equivalent or superior to bolus oxytocin for prevention of postpartum hemorrhage [1, 4].

## 5. Pharmacokinetics and Routes of Administration

### 5.1 Absorption

Carbetocin is administered clinically by intravenous or intramuscular injection for the uterotonic indication and by intranasal spray for the Prader-Willi syndrome application. The compound is not orally bioavailable (peptide bonds are hydrolyzed by gastrointestinal proteases despite the thioether stabilization of the macrocycle). Onset of uterine contractions is within 2 minutes of either intravenous or intramuscular administration. Intramuscular bioavailability is approximately 80 percent relative to the intravenous route [7, 15]. Intranasal bioavailability for central nervous system delivery has not been precisely quantified but is estimated at 5 to 15 percent of the administered dose reaching cerebrospinal fluid based on analogous peptide studies.

### 5.2 Distribution

Volume of distribution after intravenous administration is approximately 20 to 25 liters (approximately 0.3 liters per kilogram), consistent with predominantly extracellular distribution. Plasma protein binding has not been extensively characterized but is estimated at less than 50 percent based on the hydrophilic peptide character. The compound distributes to the uterus and mammary gland where oxytocin receptors are expressed at high density during the peripartum period [7].

### 5.3 Metabolism and elimination

Carbetocin is cleared principally by enzymatic degradation. The thioether bridge prevents disulfide reduction, and the deaminated N-terminus prevents aminopeptidase attack on the ring portion; however, C-terminal carboxypeptidases can progressively cleave the tail residues (Gly-NH<sub>2</sub>, then Leu, then Pro) to generate shorter-chain metabolites with reduced or absent uterotonic activity. Two principal metabolites have been identified in vitro: des-Gly-NH<sub>2</sub>-carbetocin (metabolite I) and des-Leu-Gly-NH<sub>2</sub>-carbetocin (metabolite II), both of which retain measurable but re-

duced oxytocin receptor binding [18]. Renal clearance of intact carbetocin accounts for a minor fraction of elimination; the predominant route is enzymatic degradation in plasma and tissues.

## 5.4 Half-life and pharmacokinetic parameters

After intravenous administration of 100 microgram, carbetocin shows biphasic elimination: a rapid distribution phase (half-life approximately 3 to 4 minutes) and a terminal elimination phase (geometric mean half-life approximately 33 minutes). After intramuscular administration of 100 microgram, the terminal half-life extends to approximately 55 minutes owing to continued absorption from the injection depot [7]. The pharmacokinetics are linear over the dose range of 8 to 800 microgram intravenous. The duration of pharmacodynamic effect (rhythmic uterine contractions) substantially exceeds the plasma half-life, lasting approximately 60 to 120 minutes after a single 100 microgram dose, consistent with the slow receptor dissociation and receptor sequestration mechanism [1, 2].

## 5.5 Special populations

Pharmacokinetic data in renal impairment, hepatic impairment, and pediatric populations are limited. The peptide clearance mechanism (enzymatic degradation rather than hepatic CYP-mediated metabolism) suggests that hepatic impairment would have minimal effect on carbetocin pharmacokinetics. The compound is not used in pregnancy (contraindicated for induction of labor) and is administered only postpartum. Pediatric pharmacokinetics for the intranasal PWS application have been characterized in the CARE-PWS trial population (ages 7 to 18) but detailed PK parameters have not been published separately [6].

## 6. Preclinical Pharmacology

### 6.1 In vitro uterotonic activity

In vitro studies on isolated myometrial strips from pregnant or estrogen-primed rats demonstrate that carbetocin is a partial agonist with approximately one-thirtieth the contractile potency of oxytocin on a molar basis. The EC<sub>50</sub> for carbetocin-induced contraction of rat uterine strips is approximately 48 nanomolar compared to 5.6 nanomolar for oxytocin, and the maximum contractile response (E<sub>max</sub>) is approximately 50 percent of the oxytocin maximum [18, 19]. Despite the lower in vitro potency, the in vivo duration of uterotonic effect is substantially greater owing to the metabolic stability of carbetocin, and the clinical dose of 100 microgram produces uterotonic efficacy equivalent to 5 to 10 IU of oxytocin infusion [1].

### 6.2 In vivo uterotonic duration

In the postpartum rat model, a single subcutaneous injection of carbetocin produces sustained rhythmic uterine contractions for 60 to 90 minutes, compared to 10 to 15 minutes for an equimolar dose of oxytocin [11, 19]. The duration-of-effect advantage is approximately 6- to 8-fold in rodent models and 4- to 6-fold in human postpartum clinical observations [1, 2].

### 6.3 Milk ejection

Carbetocin stimulates milk ejection in lactating animals through activation of oxytocin receptors on myoepithelial cells of the mammary alveoli. This effect underlies the veterinary application in dairy cattle (prevention of mastitis through complete milk ejection) and is observed clinically in postpartum women receiving carbetocin, where early initiation of lactation has been reported as a secondary benefit [15].

## 6.4 Neurobehavioral models

In rodent models relevant to the Prader-Willi syndrome application, intranasal and subcutaneous carbetocin has been evaluated for effects on feeding behavior, social interaction, and anxiety-like behavior. The *Magel2*-null mouse (a model of PWS with deletion of the *MAGE-like 2* gene) shows reduced oxytocin neuron number and hyperphagia; intranasal carbetocin administration in neonatal *Magel2*-null mice has been reported to improve survival and feeding behavior [20]. However, in other rodent behavioral models, carbetocin has shown inconsistent prosocial effects. A study in the BTBR mouse model of autism-like behavior (Harony-Nicolas et al. 2017) found that carbetocin failed to exert prosocial effects, in contrast to an oxytocin metabolite that did produce behavioral improvement, suggesting that the functional selectivity of carbetocin (absence of beta-arrestin signaling) may limit its prosocial efficacy in some contexts [21].

## 6.5 Sensorimotor gating

Caldwell et al. (2010) evaluated carbetocin in mouse models of sensorimotor gating (prepulse inhibition of startle). Carbetocin showed no significant effect on PPI measures, and the data did not support the use of carbetocin as an antipsychotic-like compound [22]. This negative finding is relevant to distinguishing the potential clinical applications of carbetocin from broader oxytocin-system interventions that target social cognition and psychosis-related endpoints.

## 7. Clinical Evidence Base

### 7.1 Postpartum hemorrhage: cesarean delivery

The registration trials for carbetocin in cesarean delivery compared single-dose intravenous carbetocin 100 microgram to standard oxytocin infusion (typically 5 IU bolus followed by 10 to 40 IU in crystalloid over several hours). Multiple randomized controlled trials demonstrated that single-dose carbetocin produced equivalent prevention of uterine atony and reduced the need for additional uterotonic agents [1, 2, 23]. A 2018 meta-analysis of randomized controlled trials in cesarean deliveries (Voon et al. 2018) reported that carbetocin was associated with significant reductions in postpartum hemorrhage (relative risk 0.79; 95 percent confidence interval 0.66 to 0.94), use of additional uterotonics (relative risk 0.57; 95 percent CI 0.49 to 0.65), and need for blood transfusion (relative risk 0.31; 95 percent CI 0.15 to 0.64) compared to oxytocin [24]. A 2022 systematic review and meta-analysis (Sun et al. 2022) confirmed the superiority of carbetocin over oxytocin for cesarean delivery with comparable safety [25].

### 7.2 Postpartum hemorrhage: vaginal delivery (CHAMPION trial)

The WHO CHAMPION trial (Widmer et al. 2018) is the landmark study establishing carbetocin for vaginal delivery [4]. The trial enrolled 29,645 women delivering vaginally at 23 hospitals across 10 countries. Women were randomized to receive intramuscular heat-stable carbetocin 100 microgram or intramuscular oxytocin 10 IU immediately after vaginal birth. The primary composite outcome (blood loss of at least 500 mL or use of additional uterotonic agents) occurred in 14.5 percent of the carbetocin group and 14.4 percent of the oxytocin group (relative risk 1.01; 95 percent CI 0.95 to 1.06), meeting the prespecified noninferiority margin. There were no significant differences between groups in blood loss of at least 1000 mL (1.51 percent versus 1.45 percent), use of additional uterotonics alone (12.0 percent versus 12.1 percent), or adverse effects. The trial established heat-stable carbetocin as a clinically equivalent alternative to oxytocin with the critical operational advantage of room-temperature stability [4].

A secondary analysis of the CHAMPION trial (Ghosh et al. 2023) evaluated outcomes specifically in women at elevated risk for postpartum hemorrhage (prior PPH, grand multiparity, overdistended uterus) and confirmed similar efficacy in this high-risk subgroup [26].

## 7.3 Prader-Willi syndrome: Phase 2

Dykens et al. (2018) published the Phase 2 randomized placebo-controlled trial of intranasal carbetocin in 37 participants aged 10 to 18 with genetically confirmed PWS [5]. Participants received intranasal carbetocin (titrated to effect) or placebo three times daily for 14 days. The carbetocin group showed statistically significant reductions in the Hyperphagia Questionnaire for Clinical Trials (HPWSQ-R) total score at study end (change from baseline: carbetocin -15.6 versus placebo -8.9;  $p < 0.05$ ). Secondary endpoints including food-related behavior and global clinical impression showed numerical but not statistically significant improvement. The compound was well tolerated with no serious adverse events.

## 7.4 Prader-Willi syndrome: CARE-PWS Phase 3

Kimonis et al. (2023) reported the CARE-PWS Phase 3 trial, a randomized double-blind placebo-controlled study in 130 participants aged 7 to 18 with genetically confirmed PWS [6]. Participants were randomized to 9.6 mg, 3.2 mg, or placebo three times daily during an 8-week placebo-controlled period followed by a 56-week open-label extension. The 3.2 mg dose produced clinically meaningful improvements in hyperphagia (HPWSQ-R) and anxiousness and distress behaviors, with numerical improvement versus placebo on 11 of 12 specified primary and secondary endpoints. However, the primary endpoint did not achieve statistical significance at the prespecified threshold. The 9.6 mg dose did not show superior efficacy to the 3.2 mg dose, suggesting an inverted-U dose-response relationship. The compound was well tolerated across both dose groups with no dose-limiting toxicities. Despite positive signals, the FDA did not grant approval for this indication, and the regulatory path forward remains uncertain as of the most recent monograph revision.

## 7.5 Dose-finding studies

Butwick et al. (2010) conducted a randomized dose-finding study of carbetocin at elective cesarean delivery, evaluating doses from 2 to 100 microgram intravenous [27]. The ED90 (dose producing adequate uterine tone in 90 percent of patients) was

estimated at 14.8 microgram, substantially below the registered 100 microgram dose. The registered dose therefore provides a substantial safety margin and ensures near-complete uterotonic coverage across the patient population.

## 8. Sourcing and Quality Verification

Pharmaceutical-grade carbetocin (Duratocin, Pabal brand or WHO-prequalified generic) is the highest quality source for clinical research applications. The pharmaceutical-grade material is supplied as 100 microgram/mL solution in single-use glass ampoules for intravenous or intramuscular injection. WHO prequalification was granted to Ferring's heat-stable carbetocin formulation in 2019. Multiple generic manufacturers have achieved WHO prequalification for the heat-stable formulation for supply in low- and middle-income countries.

Research-grade carbetocin is supplied by multiple peptide synthesis companies (CPC Scientific, MedChemExpress, Bachem, Tocris, Cayman Chemical, Santa Cruz Biotechnology, BOC Sciences) at greater than 95 percent purity by HPLC. Supply is in milligram to gram quantities as the free base or acetate salt. Pricing is moderate for a synthetic peptide: approximately \$100 to \$500 per 10 mg depending on quantity and supplier.

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

- Reversed-phase HPLC area-percent purity (greater than 95 percent; pharmaceutical-grade standard is greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (expected  $[M+H]^+$  989.49;  $[M+2H]^{2+}$  495.25)
- Peptide content determination (nitrogen analysis or amino acid analysis) to distinguish between lyophilizate mass and active peptide content
- Endotoxin testing (Limulus amebocyte lysate assay) for any parenteral research application
- Residual solvent analysis (trifluoroacetic acid from HPLC purification; acetonitrile from mobile phase)
- Water content (Karl Fischer titration) for hygroscopic lot assessment

Third-party analytical laboratories can provide independent confirmation of vendor certificates of analysis. The peptide nature of carbetocin makes it susceptible to degradation during storage; investigators should confirm potency at the time of use

if the material has been stored for more than 6 months at conditions other than minus 20 degrees Celsius.

## 9. Reconstitution and Handling

Carbetocin is supplied as a lyophilized powder (research-grade) or as a ready-to-use aqueous solution (pharmaceutical-grade ampoules). For research applications requiring reconstitution:

**Aqueous reconstitution:** Dissolve lyophilized carbetocin in sterile water for injection, normal saline, or phosphate-buffered saline at pH 5 to 7. The peptide is freely soluble at concentrations up to 10 mg/mL. Stock solutions should be prepared at 1 mg/mL for convenient dilution. For in vitro receptor binding or cell-based assays, dimethyl sulfoxide may be used as a co-solvent at final concentrations below 0.1 percent.

**Storage of reconstituted solutions:** Aqueous solutions are stable for 7 days at 2 to 8 degrees Celsius and for at least 30 days when frozen at minus 20 degrees Celsius. The heat-stable pharmaceutical formulation (succinate buffer, pH 5.45, with methionine antioxidant) maintains greater than 95 percent potency for 36 months at 30 degrees Celsius [13]. Research investigators seeking extended stability should formulate reconstituted carbetocin at pH 5 to 5.5 with 0.1 percent methionine to prevent oxidation.

**Aliquoting:** Single-use aliquoting is recommended to avoid freeze-thaw degradation. Although the thioether linkage is stable to freeze-thaw, the peptide bonds in the tail region may accumulate deamidation (Asn to Asp conversion) with repeated cycling.

**Light protection:** Not strictly required but recommended for long-term storage. The O-methyltyrosine chromophore absorbs at 275 nanometers and could theoretically undergo photodegradation with prolonged UV exposure.

**Incompatibilities:** Avoid strongly alkaline solutions (pH greater than 8) which accelerate asparagine deamidation. Avoid oxidizing agents which can convert the thioether to sulfoxide. Avoid contact with heavy metal ions (copper, iron) which catalyze oxidative degradation of peptides.

# 10. Stack Interactions and Combinations

Carbetocin interacts with several drug classes through its oxytocin receptor pharmacology and its peptide nature. Investigators conducting research with carbetocin should consider:

**Prostaglandins (misoprostol, dinoprostone, carboprost):** Prostaglandins potentiate the uterotonic effect of oxytocin receptor agonists. Concurrent administration can produce excessive uterine contraction, hypertonia, or tetanic contraction. The combination is contraindicated in clinical practice; research applications requiring both agents should use sequential rather than concurrent administration with appropriate washout intervals [28].

**Ergot alkaloids (methylergonovine, ergonovine):** Ergot-derived uterotonics produce sustained smooth muscle contraction through serotonin and alpha-adrenergic receptor mechanisms. Combination with carbetocin may enhance blood pressure elevation. The combination is used clinically only as rescue therapy for refractory postpartum hemorrhage [28].

**Vasopressin analogs (desmopressin, terlipressin):** Carbetocin does not activate vasopressin receptors, but the combination with vasopressin agonists has not been studied and should be approached with caution regarding potential additive hemodynamic effects.

**Inhaled anesthetics (sevoflurane, desflurane, isoflurane):** Volatile anesthetic agents produce dose-dependent uterine relaxation. This interaction is clinically relevant during cesarean delivery under general anesthesia, where higher carbetocin or oxytocin doses may be required to overcome anesthetic-induced myometrial relaxation [29].

**Epidural and spinal anesthetics:** No pharmacokinetic interaction. The sympathetic block produced by neuraxial blockade may potentiate carbetocin-induced hypotension. The combination is standard clinical practice for cesarean delivery; hemodynamic monitoring is routine.

**CYP enzyme interactions:** Carbetocin is not metabolized by cytochrome P450 enzymes and does not inhibit or induce CYP isoforms. No CYP-mediated drug-drug interactions are expected.

**Intranasal formulation considerations (PWS application):** Concurrent intranasal decongestants (oxymetazoline, xylometazoline) may alter nasal mucosal blood flow and absorption. Concurrent intranasal corticosteroids (fluticasone, mometasone) are unlikely to interact but may alter mucosal permeability with chronic use.

# 11. Adverse Events and Safety

## 11.1 Common adverse events (uterotonic indication)

The principal adverse events following 100 microgram intravenous or intramuscular carbetocin for postpartum hemorrhage prevention are [8, 9]:

- Nausea (15 to 35 percent)
- Vomiting (5 to 15 percent)
- Abdominal pain or cramping (10 to 20 percent, reflecting uterotonic activity)
- Flushing and warmth (10 to 25 percent)
- Headache (5 to 15 percent)
- Pruritus (5 to 10 percent)
- Tremor (3 to 8 percent)
- Metallic taste (1 to 5 percent)

These frequencies are comparable to those observed with standard-dose oxytocin (5 to 10 IU). A systematic review and meta-analysis of side effects (2021) reported no statistically significant differences between carbetocin and oxytocin for any individual adverse event category [9]. The gastrointestinal side-effect burden is lower with carbetocin than with the combination of oxytocin plus ergometrine (Syntometrine), which has a substantially higher emesis rate.

## 11.2 Cardiovascular effects

Both oxytocin and carbetocin produce transient cardiovascular effects through direct vasodilation and through oxytocin receptor activation in the myocardium [30]. Reported cardiovascular effects include:

- Hypotension (transient, 5 to 15 percent; typically a 10 to 20 mmHg systolic reduction lasting 2 to 5 minutes)
- Tachycardia (reflex, 5 to 10 percent; typically 10 to 20 beats per minute increase)
- Chest pain (rare, 1 to 3 percent)

A prospective double-blind randomized study comparing cardiovascular effects of oxytocin and carbetocin at cesarean section using noninvasive pulse wave analysis demonstrated indistinguishable hemodynamic profiles between the two agents, with neither producing alarmingly adverse cardiovascular effects in hemodynamically stable patients [30]. The hypotensive effect is clinically relevant in hypovolemic patients or in those with compromised cardiac function; the intravenous bolus should be administered slowly (over 1 minute) rather than as a rapid push in such patients.

### 11.3 Adverse events in Prader-Willi syndrome application

The CARE-PWS Phase 3 trial reported favorable tolerability of intranasal carbetocin at 3.2 mg and 9.6 mg three times daily for 8 weeks [6]. Adverse events were generally mild, with headache, nasal discomfort, and rhinorrhea being the most common treatment-emergent events. No serious drug-related adverse events were reported. The intranasal route avoids the uterotonic effects that are the principal pharmacodynamic action (and adverse-event source) of the injectable preparation.

### 11.4 Contraindications

Carbetocin is contraindicated in the following settings [28]:

- During pregnancy and labor (risk of uterine hyperstimulation, fetal distress, uterine rupture)
- Known hypersensitivity to carbetocin or oxytocin
- Severe cardiovascular disease, particularly severe pre-eclampsia or eclampsia
- Epilepsy (theoretical risk of seizure threshold reduction, extrapolated from high-dose oxytocin data)

Overdose or repeated dosing carries risk of uterine hyperstimulation, water intoxication (less likely than with oxytocin given the absence of V2 receptor agonism), and cardiovascular compromise.

### 11.5 Reproductive safety

The compound is administered only in the immediate postpartum period for the uterotonic indication and is therefore not relevant to embryonic or fetal exposure. The intranasal PWS application has been studied in children aged 7 to 18; no repro-

ductive toxicity signals have been identified.

## 12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative uterotonics and oxytocin-system compounds against carbetocin, evaluated on five competency standards: novelty, effect size, promising potential (clinical utility and trajectory), side-effect profile, and overall validation.

### 12.1 Oxytocin (Pitocin, Syntocinon)

**Mechanism:** Full agonist at the oxytocin receptor with activity at vasopressin V1a and V2 receptors. Recruits both Gq and beta-arrestin pathways. The endogenous reference compound.

**Clinical position:** The global standard of care for prevention and treatment of postpartum hemorrhage. WHO Essential Medicine. Administered as intravenous infusion (5 to 40 IU in crystalloid) or intramuscular injection (10 IU). Requires cold-chain storage (2 to 8 degrees Celsius) and degrades within days to weeks at ambient temperatures in tropical climates [4, 31].

**Novelty:** None (endogenous hormone, clinical use since the 1950s).

**Effect size:** The reference standard for uterotonic efficacy. Postpartum hemorrhage prevention rate approximately 85 to 90 percent at adequate doses. The CHAMPION trial established carbetocin as noninferior to oxytocin for vaginal delivery [4].

**Promising potential:** Maximal (established global standard). Limitations are cold-chain requirement, short half-life requiring infusion rather than bolus for sustained effect, and water-retention risk at high doses from V2 receptor agonism.

**Side-effect profile:** Nausea, vomiting, hypotension, tachycardia, water intoxication (V2 agonism at high doses producing hyponatremia), uterine hyperstimulation with excessive dosing. Comparable to carbetocin for most adverse events; the V2-mediated water retention is a disadvantage relative to carbetocin [9].

**Overall validation:** Maximum. The most extensively studied uterotonic in human medicine. All other agents are compared against this reference.

**Comparison to carbetocin:** Carbetocin's advantages over oxytocin are: single-dose convenience (no infusion required), longer duration of action, heat stability (eliminates cold-chain requirement), and absence of vasopressin V2 agonism (no water-retention risk). Oxytocin's advantages are: decades of safety data, universal availability, extremely low cost (\$0.10 to \$1.00 per dose), and titratable dosing for treatment (not just prevention) of hemorrhage.

## 12.2 Misoprostol

**Mechanism:** Synthetic prostaglandin E1 analog acting at EP2 and EP3 receptors on myometrium to produce uterine contraction. Oral, sublingual, and rectal routes available.

**Clinical position:** The most important alternative uterotonic for settings where injectable oxytocin is unavailable. WHO Essential Medicine for prevention of postpartum hemorrhage where oxytocin is not available. Oral/sublingual dose 600 microgram. Also used for cervical ripening, labor induction, medical abortion, and treatment of gastric ulcers [32].

**Novelty:** Low (prostaglandin E1 analog, clinical use since the 1980s for gastric ulceration, repurposed for obstetric indications in the 1990s).

**Effect size:** Inferior to oxytocin for postpartum hemorrhage prevention. A Cochrane systematic review reported that misoprostol is less effective than injectable uterotonics for PPH prevention (relative risk of blood loss greater than 1000 mL: 1.33 with misoprostol versus oxytocin). However, it is substantially more effective than placebo and is the only oral uterotonic [32].

**Promising potential:** High for resource-limited settings where injectable agents and cold chains are unavailable. The oral route and ambient temperature stability are unique advantages. Limited by inferior efficacy and higher side-effect burden compared to injectable oxytocin or carbetocin.

**Side-effect profile:** Higher incidence of shivering (40 to 60 percent), pyrexia (20 to 40 percent), diarrhea (5 to 15 percent), and nausea/vomiting compared to oxytocin or carbetocin. The thermoregulatory effects are a class effect of prostaglandin E analogs and limit acceptability [32].

**Overall validation:** High. Extensively studied in randomized trials. Cochrane reviews confirm utility as second-line or resource-limited alternative.

**Comparison to carbetocin:** Carbetocin is superior in efficacy and side-effect profile for PPH prevention. Misoprostol's advantage is oral availability and extremely low cost. Heat-stable carbetocin addresses the cold-chain issue that previously made misoprostol the default alternative in low-resource settings, but carbetocin remains injectable (requiring syringes and trained personnel).

## 12.3 Ergonovine/Methylergonovine (Methergine)

**Mechanism:** Ergot alkaloid acting at serotonin (5-HT<sub>2</sub>) and alpha-adrenergic receptors on myometrial smooth muscle to produce sustained tetanic uterine contraction, distinct from the rhythmic contractions produced by oxytocin receptor agonists.

**Clinical position:** Historical second-line uterotonic for treatment of postpartum hemorrhage. Intramuscular 0.2 mg. Also used in the fixed combination Syntometrine (oxytocin 5 IU plus ergometrine 0.5 mg). Declining in clinical use owing to hypertension risk and the availability of safer alternatives [33].

**Novelty:** None (ergot alkaloid derivatives, clinical use since the 1930s).

**Effect size:** Produces reliable and sustained uterine contraction. Efficacy for PPH prevention is similar to oxytocin in systematic reviews, though with higher adverse event rates. The tetanic contraction pattern is useful for treatment of active hemorrhage where the uterus remains atonic despite oxytocin [33].

**Promising potential:** Declining. Contraindicated in hypertensive disorders (pre-eclampsia, gestational hypertension), which affect 5 to 10 percent of pregnancies globally. The combination Syntometrine has been largely replaced by single-agent oxytocin or carbetocin in many formularies.

**Side-effect profile:** Hypertension (20 to 30 percent, clinically significant in pre-eclampsia), nausea and vomiting (30 to 50 percent), peripheral vasoconstriction, rare coronary vasospasm and myocardial ischemia. Substantially worse side-effect profile than carbetocin [33].

**Overall validation:** Moderate to high. Historical use and efficacy are well established; safety concerns have driven displacement by newer agents.

**Comparison to carbetocin:** Carbetocin is substantially safer (no hypertension risk, no coronary vasospasm risk) and more convenient (single bolus) than ergot alkaloids. Ergot alkaloids retain a role in treatment of refractory atony (rescue therapy) but are inferior to carbetocin for prophylaxis.

## 12.4 Atosiban (Tractocile)

**Mechanism:** Selective oxytocin receptor antagonist with weak vasopressin V1a antagonist activity. Used as a tocolytic (inhibition of premature labor) rather than as a uterotonic.

**Clinical position:** Registered in approximately 70 countries (not FDA-approved) for tocolysis in threatened preterm labor between 24 and 33 weeks gestation. Intravenous bolus 6.75 mg followed by infusion 18 mg/hour for 3 hours then 6 mg/hour for up to 45 hours [34].

**Novelty:** Moderate (the only marketed OTR antagonist; mechanism is opposite to carbetocin).

**Effect size:** Comparable to beta-agonist tocolytics (ritodrine, terbutaline) for delaying delivery by 48 hours with substantially fewer maternal cardiovascular side effects. Does not reduce overall preterm birth rate or improve neonatal outcome [34].

**Promising potential:** Moderate. Established role in European tocolytic practice. Not available in the United States. Research interest in OTR antagonist pharmacology continues.

**Side-effect profile:** Favorable. Nausea, headache, dizziness at rates comparable to placebo. The absence of cardiovascular effects is the principal advantage over beta-agonist tocolytics.

**Overall validation:** Moderate. Established in European clinical practice with extensive randomized trial data.

**Comparison to carbetocin:** Atosiban and carbetocin are pharmacological opposites (antagonist versus agonist at the same receptor) with opposite clinical applications (tocolysis versus uterotonic). They are complementary rather than competitive compounds in the oxytocin receptor pharmacology space. Both illustrate the feasibility of selective OTR modulation as a clinical strategy.

## 12.5 Intranasal Oxytocin (Syntocinon Spray, research preparations)

**Mechanism:** Full agonist at the oxytocin receptor delivered intranasally for central nervous system effects. The intranasal route delivers oxytocin to CSF via olfactory and trigeminal nerve transport.

**Clinical position:** Registered in some jurisdictions for promotion of milk let-down (lactation support). Extensively investigated in clinical research for social cognition, autism spectrum disorder, anxiety disorders, pain, and Prader-Willi syndrome. Not FDA-approved for any neurobehavioral indication [14, 35].

**Novelty:** Low (endogenous peptide, intranasal delivery).

**Effect size:** Inconsistent across clinical trials in autism and social cognition. A large Phase 3 trial (NEJM 2021) of intranasal oxytocin in children with autism failed to demonstrate improvement in social responsiveness [35]. Effects on acute social cognition tasks (single-dose studies) are modest. In PWS, intranasal oxytocin has shown mixed results with some positive and some negative trials.

**Promising potential:** Moderate for specific indications (PWS, possibly social anxiety) but diminished after the negative Phase 3 autism trial. The rapid metabolism of native oxytocin (half-life 3 to 4 minutes) limits sustained central effects, which is the rationale for carbetocin as a longer-acting alternative.

**Side-effect profile:** Generally well tolerated. Nasal irritation, headache, rhinitis at mild frequency. Chronic intranasal oxytocin may produce paradoxical reductions in social behavior in some contexts (Huang et al. 2014) [14].

**Overall validation:** Moderate. Extensive research literature but inconsistent clinical translation. The negative autism Phase 3 has substantially reduced enthusiasm.

**Comparison to carbetocin:** Carbetocin has several advantages over intranasal oxytocin for central applications: longer half-life at the receptor (sustained engagement), absence of vasopressin receptor cross-reactivity, and potentially more favorable CNS pharmacokinetics owing to enzymatic resistance. The CARE-PWS Phase 3 results for carbetocin in PWS are more positive than the available intranasal oxytocin data in the same population, supporting the hypothesis that longer-acting receptor engagement is therapeutically important. The principal uncertainty is whether carbetocin's biased signaling (Gq without beta-arrestin) limits its prosocial efficacy relative to oxytocin's full-spectrum signaling.

## 12.6 Comparator summary

The five compounds occupy distinct positions in the uterotonic and oxytocin-system pharmacology space. **Oxytocin** is the universal reference standard with maximal validation but operational limitations (cold chain, short half-life, V2 agonism). **Misoprostol** fills the critical niche of oral uterotonic availability in resource-limited settings but at the cost of inferior efficacy and higher side-effect burden. **Ergot alkaloids** are legacy uterotonics with sustained efficacy for rescue therapy but unacceptable hypertension risk for prophylaxis. **Atosiban** represents the complementary OTR antagonist approach for tocolysis. **Intranasal oxytocin** is the reference compound for central oxytocin-system modulation with inconsistent clinical translation.

Carbetocin occupies a distinctive position in this landscape as the only compound combining: (a) registered uterotonic efficacy equivalent to oxytocin from a single dose; (b) heat stability eliminating cold-chain dependence; (c) selective OTR agonism without vasopressin receptor activation; (d) functional selectivity (biased Gq signaling) representing a novel pharmacological mechanism; and (e) a viable clinical development program for central neurobehavioral applications (PWS hyperphagia). The principal limitations are cost (substantially higher than oxytocin), injectable-only administration for the uterotonic indication, and the incomplete regulatory success of the intranasal PWS program.

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