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Update on the efficiency and safety of orally administered nasal decongestants

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ABSTRACT

Nasal congestion leading to obstruction is one of the main symptoms in acute rhinosinusitis (common cold), other upper respiratory infections and allergic rhinitis. The EPOS 2020 guidelines place oral decongestants as an efficient therapy for the relief of nasal obstruction.

In Romania, there are more than 50 available nasal decongestants, so it is very important for practitioners from all medical domains to be aware of recent data regarding their effectiveness and safety profile. Recent concerns raised by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) regarding the efficacy and safety of pseudoephedrine (PSE) and phenylephrine (PHE) emphasize the need for informed decision-making in prescribing. Notably, there were concerns raised about the association between PSE, reversible cerebral vasoconstriction syndrome (RCVS) and posterior reversible encephalopathy syndrome (PRES).

EMA's safety committee, Pharmacovigilance Risk Assessment Committee (PRAC), recently recommended measures to minimize risks of serious side effects when using medicines containing PSE. PRAC recommends that medicines containing PSE should not be used in patients with severe or uncontrolled hypertension and severe acute or chronic kidney disease or failure. Additionally, PRAC recommends healthcare professionals to counsel patients to discontinue the use of such medicines promptly and seek medical assistance if they experience symptoms suggesting PRES or RCVS, such as sudden onset of severe headache, confusion, vomiting, visual disturbances or seizures.

While effectiveness of oral PSE is confirmed by clinical studies, expert consensus is unfavorable to PHE. Both in vitro and in vivo clinical pharmacology data indicate that neither the recommended doses nor higher doses of oral PHE demonstrate efficacy in alleviating symptoms of nasal congestion.

Keywords: nasal congestion, rhinosinusitis, reversible cerebral vasoconstriction syndrome, posterior reversible encephalopathy syndrome

PRESENT SITUATION

The common cold, defined as acute rhinosinusitis with symptoms lasting less than 10 days, is one of the most frequent conditions, in adults (2-5 episodes/year) but mostly in schoolchildren (7-10 episodes/year). Nasal congestion is one of the main symptoms in acute rhinosinusitis (common cold), in other upper respiratory infections, as well as in allergic rhinitis. Most of the respiratory infections are of viral etiology, so they do not need antibiotic therapy. The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 guidelines mentions decongestants as an efficient therapy for the relief of nasal obstruction, mainly in oral preparations. There are also several topical nasal decongestants available, but their efficiency is limited by the significant issue of rebound nasal congestion, which develops a few days after initiating the treatment [1].

The choice of effective oral decongestants as self-care options is limited to pseudoephedrine (PSE) and phenylephrine (PHE)-containing products. Available data suggest that PSE is a better option

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than PHE in terms of efficiency. The dense sympathetic innervation of the blood vessels in the nasal airways and their high sensitivity to sympathomimetics makes that the decongestive effect of these drugs is achieved at doses which have minimal effect on the cardiovascular system [2].

While antihistamines are also commonly used in oral preparations to alleviate symptoms of common cold, it must be noted that they have no effect on nasal obstruction [1].

Acute reversible nasal obstruction has an important impact on the quality of life, as patients are forced to breathe through the mouth, while losing some of the smell and taste sensibility. The direct healthcare costs of common cold are considerable, and the over-prescription of antibiotics is an important public health concern. Because nasal congestion contributes to high rates of absenteeism, as well as underperforming at the workplace or school, the common cold has also important indirect costs.

It is generally accepted that self-care is central to the management of acute uncomplicated viral respiratory infections, mainly acute rhinosinusitis, so it is important that patients have access to self-care options, such as oral PSE-containing products. Several guidelines, such as the EPOS 2020 emphasize the important role of self-care, including use of decongestants and avoidance of antibiotics in these patients. Lacking options for self-care decongestion would increase the burden on primary care services, as well as the overuse of antibiotics, while favouring absenteeism.

FDA ADVISORY COMITTEE ON THE EFFICACY OF PSEUDOEPHEDRINE AND PHENYLEPHRINE

For over half a century, PSE and phenylephrine PHE have been used to relieve nasal congestion by their vasoconstrictor effect. These substances are available in pharmacies in either oral or local intranasal forms.

During this time, PSE has proven its effectiveness in alleviating nasal congestion. There are numerous studies which confirmed benefits of PSE for treating nasal obstruction, sinusitis, and opening the Eustachian tube [3-6].

Nonetheless, PSE comes with a significant drawback as it can be used in the production of methamphetamine due to their structural similarity.

To mitigate this issue and restrict methamphetamine production and consumption, the FDA made a decision in 2007 to relocate PSE-containing products behind pharmacy counters. As businesses prefer products readily accessible on shelves, they introduced new formulations containing another longstanding over-the-counter active ingredient, phenylephrine (PHE) [7].

On September 11th and 12th, 2023, the FDA convened a Non-prescription Advisory Committee meeting to deliberate on the efficacy of oral PHE, both as a standalone ingredient and when combined with other substances. Advisory committees offer unbiased guidance and suggestions to the FDA. The agency will take into account the input from this advisory committee prior to making any decisions regarding the status of oral PHE.

The committee thoroughly examined the existing data regarding the effectiveness of PHE, and their consensus was that the current scientific evidence does not substantiate the recommended dosage of orally administered PHE as an effective nasal decongestant. However, it's important to note that neither the committee nor the FDA expressed any reservations regarding the safety of oral PHE.

The committee also determined that the initial studies used to validate the drug's effectiveness were, at best, inconclusive and raised concerns about potential methodological, statistical, and data integrity issues.

Expert consensus is uniformly unfavorable to oral PHE regarding its effectiveness. Both in vitro and in vivo clinical pharmacology data indicate that neither the recommended doses nor higher doses of oral PHE demonstrate efficacy in alleviating symptoms of nasal congestion.

PHE is one of the many over-the-counter medications that the FDA deemed *"generally recognized as safe and effective"* (GRASE) when used in accordance with product labelling. If the FDA were to determine that oral PHE lacks effectiveness, the initial step would be to propose an order for its removal from the OTC monograph. Subsequently, the public would have the opportunity to comment on the proposed order. After carefully evaluating the comments, if the FDA maintained its conclusion that PHE is ineffective, a final order would be issued, effectively removing this ingredient from the monograph, thereby no longer categorizing PHE as GRASE. The FDA would then collaborate closely with producers to reformulate products as necessary to ensure the availability of safe and effective options for treating cold or allergy symptoms.

It is important to reiterate that this conclusion is only related to the oral formulations of PHE and not to the nasal spray form [8].

EMA ON THE ASSOCIATION BETWEEN PSEUDOEPHEDRINE, PRES AND RCVS

In early 2023, the European Medicines Agency Pharmacovigilance Risk Assessment Committee (EMA PRAC), EMA's committee responsible for assessing and monitoring the safety of human medicines, initiated an assessment of the safety of prod-

ucts containing PSE. This action was prompted by growing apprehension regarding its potential link with posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS). Recent data from pharmacovigilance databases and medical literature indicates a small number of PRES and RCVS cases in individuals who had used PSE-containing products [9].

PRES and RCVS are rare neurologic conditions that involve cerebral ischemia, which may lead to serious or life-threatening complications, particularly in susceptible patients. Typical symptoms of both conditions include headache, nausea, and seizures. With rapid diagnosis and treatment, however, symptoms of PRES and RCVS resolve in most cases.

Given the serious implications of these conditions, PRAC has embarked on a comprehensive assessment of available data. In December 2023, it released an official statement containing recommendations to minimize the risk of serious side effects while using medicines containing PSE. PRAC's official statement advises against the use of medicines containing PSE only in patients with uncontrolled severe hypertension or those with severe acute or chronic kidney disease. Additionally, PRAC recommends healthcare professionals to counsel patients to discontinue the use of such medicines promptly and seek medical assistance if they experience symptoms indicative of PRES or RCVS, such as sudden onset of severe headache, vomiting, confusion, seizures, or visual disturbances [9,10].

The product information for all pseudoephedrine-containing medicines will undergo an update to incorporate details about the risk of PRES and RCVS, along with the recommended precautionary measures. It's important to note that existing restrictions and warnings in the product information of these medicines already address cardiovascular and cerebrovascular ischemic risks.

Next, the PRAC's recommendations will be forwarded to the EMA's human medicines committee (CHMP), which will then adopt the Agency's final opinion on the matter.

GENERAL INFORMATION ABOUT PSEUDOEPHEDRINE AND PHENYLEPHRINE

PSE is an alkaloid extracted from plants that belong to the *Ephedra* species, *Ephedraceae* family, the most common used plant being *Ephedra sinica.* This substance has been used since ancient times for the treatment of asthma, bronchitis, fever, cough, urticaria, hypotension or edema.

PSE is widely used for alleviating nasal congestion, allergic rhinitis, as well as hay fever [11-13].

PSE is a sympathomimetic amine that indirectly stimulates the alpha adrenergic receptors, leading to the release of endogenous norepinephrine. It also directly stimulates the alpha1, alpha2 and beta adrenoreceptors in blood vessels and the heart, although this latter effect is comparatively weaker [11].

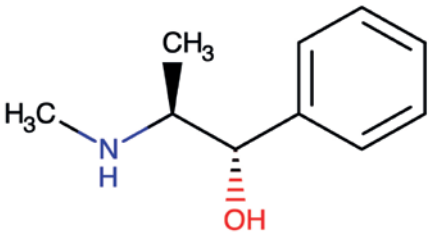

FIGURE 1. Structure of pseudoephedrine [12]

PHE is another sympathomimetic drug that specifically activates alpha1-adrenergic receptors, resulting in localized vasoconstriction and mydriasis. When absorbed into the bloodstream, it elevates both systolic and diastolic blood pressure along with an increase in peripheral vascular resistance. This effect also prompts stimulation of the vagus nerve, indirectly inducing reflex bradycardia [14].

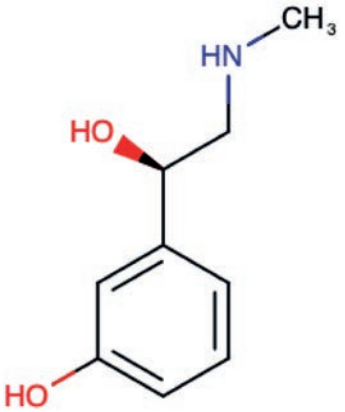

FIGURE 2. Phenylephrine structure [14]

During upper respiratory tract infections (URTIs), nasal congestion appears because of bradykinin, prostaglandine and histamine release, leading to localized vasodilation [15]. Through the activation of alpha-adrenergic receptors, PSE and PHE induce vasoconstriction, which accounts for their decongestant properties. Unfortunately, their main adverse reactions such as increasing mean arterial pressure, also derive from this vasoconstrictive effect. For PSE, stimulation of beta-adrenergic receptors, although a weak effect, can lead to positive inotropic and chronotropic effects on the heart [11,12].

Pharmacokinetics

Pseudoephedrine

PSE is easily absorbed from the gastrointestinal tract. Its bioavailability is over 90% and its absorbtion is not influenced by food [16]. The effects of PSE

starts approximately 30 minutes after oral administration. However, the peak blood concentration occurs after 1-4 hours. With the extended release formulations, the maximum concentration can be seen after 2-8 hours. The majority of PSE (55-75%) is excreted unmetabolized in the urine with only a small amount (below 1%) being N-demethylated to an inactive metabolite by the liver. The half-life of this substance is usually 6 hours, though it depends on the pH of the urine – if the urine is acidic, the half-life will be shorter, whilst if the urine is alkaline, the half life will be longer [11,12].

Phenylephrine

In contrast with oral PSE, PHE has a bioavailability of approximately 1% after oral administration, as the Nonprescription Drug Advisory Committee found recently [17]. Clinically significant systemic absorption of ophthalmic formulations is possible, especially for products with higher concentrations and in case of corneal damage. Patients receiving ophthalmic formulations of PHE should receive counseling regarding the potential risks of arrhythmia, hypertension, and rebound miosis [18].

The onset and duration of PHE's effects vary depending on the route of administration. After intravenous administration, its effects manifest within 1-3 minutes and last for 5-20 minutes. When administered intramuscularly, effects appear in 10-15 minutes and persist for 1-2 hours. Through the oral route, effects become apparent in 15-20 minutes and last for 4 hours. Ophthalmic administration yields effects in 15 minutes, lasting for 3-8 hours, while nasal administration leads to effects in less than two minutes, with a duration of 2.5-4 hours [19,20].

The primary metabolic pathways for PHE involve hepatic and intestinal monoamine oxidases, as well as cytosolic sulfotransferase SULT1A3. The major metabolite is the inactive meta-hydroxymandelic acid, with sulfate conjugates following as the next significant metabolites. Additionally, PHE can undergo metabolism to form PHE glucuronide [21].

Most of a PHE dose is found in urine (86%), comprising 16% of the unmetabolized drug, 57% of meta-hydroxymendelic acid, and 8% as sulfate conjugates [14,22,23].

Dosage

Pseudoephedrine

PSE is available in two salt forms: hydrochloride and sulfate. It is offered either as a standalone medication or in combination with other substances such as antihistamines, anti-inflammatory and antitussive drugs, in various formulations including tablets, capsules, extended release tablets, and powder for oral suspension.

The regular tablets and oral suspensions typically contain 60mg of PSE per dose, taken at intervals of 4 to 6 hours. In contrast, the 12-hour extended-release tablets contain 120mg of PSE per dose and should be taken twice a day.

In adults, the maximum recommended daily dose of PSE is 240 mg [11]. For children aged 2 or older, the prescribed dose is 1mg per kg taken four times a day, with a maximum of 60mg per day for those between the ages of 2 and 5. For children aged 6 to 12 the highest daily dose is 120mg. PSE is not recommended for children under 2 years of age. Additionally, extended-release formulations are contraindicated for children under 12.

Treatment with PSE should not exceed 5 days for adults and 3 days for children aged 15 to 18 [13,24].

Taking doses higher than the recommended amount leads to excessive stimulation of alpha and beta-adrenergic receptors, elevating the potential for toxic effects on both the central nervous system (CNS) and the cardiovascular system. Signs of overdose mirror those outlined in the adverse reactions section below.

Phenylephrine

PHE dosages vary based on the specific indication for which it is prescribed. In cases of hypotension treatment, it is administered intravenously, with an initial dose ranging from 50 to 250 mcg, followed by a maintenance dose of 0.5 to 1.4 mcg/kg/min. For adults experiencing nasal congestion, a dose of 10 mg of PHE is given every 4 hours, with a maximum daily intake of 60 mg. However, the use of PHE is contraindicated in individuals under the age of 12 [25].

Adverse reactions

Both substances share similar side effects due to the fact that the primary adverse reactions are specific to their drug class – sympathomimetics, with only a few particularities specific to each molecule.

Pseudoephedrine

Toxic effects typically manifest when increased doses are administered or when regular doses are taken at short intervals over an extended period [24]. However, individuals who are particularly sensitive to the effects of sympathomimetics may also experience these adverse effects even without the specific circumstances mentioned above.

Cardiovascular effects

Currently available data is insufficient to establish a definitive cause-and-effect relationship between the use of PSE and cardiovascular events. Some studies indicate that the drug led to a mean increase of 1.2 mmHg in systolic blood pressure, while diastolic blood pressure remained unchanged. Additionally, heart rate increased by an average of 3 beats per minute.

There is a lack of comprehensive data regarding the use of PSE in patients with secondary hyperten-

sion, cerebrovascular disease, and coronary disease [26-28].

Given that PSE acts as a sympathomimetic, causing vasoconstriction, it is reasonable to assume it could potentially lead to acute myocardial infarction. However, a study conducted in France involving 1394 patients with acute infarction did not find a significant correlation between PSE use and acute MI [29,30].

CNS effects

The use of PSE has been associated with an increased risk of stroke, attributed to its hypertensive and vasoconstrictive effects. However, to date, there have been very few documented cases of stroke directly induced by PSE administration. A study involving 1403 patients who experienced either ischemic or hemorrhagic stroke found that it was not possible to establish a definitive cause-and-effect relationship between PSE use and these events. It is important to note, however, that this study did not include patients over the age of 70, a particularly vulnerable group with the highest potential for developing a stroke after PSE administration [30].

The highest risk of stroke was reported for doses that exceeded the maximum recommended dose, but even at usual doses the risk still persists [31].

More recently, the use of PSE has been associated with two cerebral ischemic conditions: Posterior Reversible Encephalopathy Syndrome (PRES) and Reversible Cerebral Vasoconstriction Syndrome (RCVS). Consequently, in early 2023, PRAC initiated a reevaluation procedure for all drugs containing PSE [15].

PRES is a condition which manifests with severe headache, seizures, loss of vision, and loss of consciousness. These symptoms result from vasogenic edema, often localized in the posterior region of the cerebral hemispheres [32].

RCVS is defined by reversible constriction of cerebral blood vessels, leading to severe headache, focal neurologic deficits, and potential ischemic/hemorrhagic stroke or subarachnoid hemorrhage [33].

The underlying mechanisms of PRES and RCVS remain unknown, and instances of these conditions have been associated with a wide range of unrelated factors. These include the use of medications like Linezolid and Lithium, exposure to toxins (such as scorpion venom or LSD use), certain autoimmune disorders (such as rheumatoid arthritis, Crohn's disease, and SLE), pregnancy, surgical procedures, and smoking. Due to the multitude of risk factors associated with both conditions, establishing a direct link between the use of PSE and the occurrence of PRES/RCVS is challenging. From 2007 to 2023, there have been 33 documented cases of PRES and RCVS worldwide that were linked to PSE use. Among these cases, there were only two instances where, besides the use of PSE, no risk factors were identified [34,35].

Gastrointestinal effects

There have been limited reports of ischemic colitis associated with the administration of PSE, likely attributed to the vasoconstrictive effects it exerts on the blood vessels in the gastrointestinal tract. Nevertheless, the current available data is insufficient to definitively establish a cause-and-effect relationship between the use of PSE and the occurrence of ischemic colitis [36-38].

Urinary tract effects

PSE has the potential to induce urinary retention through its stimulation of alpha1A and beta receptors. The bladder neck, urethra, and prostate harbor a significant number of alpha1A receptors, and their activation leads to the contraction of muscles in these areas, aiding in maintaining bladder continence. Meanwhile, stimulation of beta adrenergic receptors prompts relaxation of the bladder muscles, increasing resistance to voiding.

Therefore, it is advisable to exercise caution when using PSE in male patients over the age of 50 and in individuals experiencing difficulties with urinary bladder voiding [39,40].

All PSE adverse reactions are summarized in Table 1.

Phenylephrine

PHE has been subject to fewer studies compared to PSE, resulting in limited available data on its adverse reactions. Nevertheless, it is reasonable to infer that its adverse reactions are very similar to those of PSE, given that both substances belong to the same class – sympathomimetics – and their toxicity is mainly class-specific.

Current data shows that when taken orally in the recommended doses, PHE does not have an impact on the cardiovascular system in people that don't have preexisting cardiovascular diseases [42,43]. However, certain studies have suggested that administering a 15 mg dose of PHE orally has led to a rise in blood pressure by 2.7 mmHg [44]. Additionally, administering high doses of phenylephrine (120-300 mg) determined an increase in blood pressure and bradycardia in healthy individuals [45]. Further research is needed to establish PHE's safety profile in patients with cardiovascular disease [43].

All PHE adverse reactions are summarized in Table 2.

Contraindications

PSE is contraindicated in case of hypersensitivity, cardiovascular diseases such as hypertension and coronary artery disease, during pregnancy or breastfeeding (as it falls under FDA category C), in children under the age of two, severe impairment of renal or liver function, diabetes, hyperthyroidism, narrow-angle glaucoma, benign prostatic hyperplasia (BPH), or when concurrently using or having used MAOIs within the past two weeks [13,41].

TABLE 1. Pseudoephedrine adverse reactions [41]

	Frequency	Adverse reactions
Cardiovascular	Rare	Tachycardia, arrythmias, palpitations, thoracic pain
	Unknown frequency	Hypertension
Pulmonary	Rare	Asthma exacerbation or hipersensitivity reaction with bronchospasm
CNS	Rare/ Less frequent	Headache, tremor, anxiety, sleep deprivation, ischemic/ hemorrhagic stroke
Psychiatric effects	Unknown frequency	Hallucinations, behavioral troubles
Gastrointestinal (GI)	Less frequent	Xerostomia, nausea, vomiting
	Unknown frequency	Ischemic colitis
Urinary tract	Unknown frequency	Urinary retention, especially in male patients with BPH
Ocular	Unknown frequency	Optic ischemic neuropathy
Dermatologic effects	Unknown frequency	Severe rashes, including acute generalized exanthematous pustulosis
	Rare	Transient rash, urticaria, pruritus, erythema, hyperhydrosis
Immune system	Very rare	Severe hypersensitivity reactions such as facial edema, angioedema, dyspnea, bronchospasm, tachycardia, hypotension, anaphylactic reactions

CNS = Central Nervous System; BPH = Benign Prostatic Hyperplasia

Frequency of adverse reactions is defined as the following convention: ***Very frequent*** *(≥1/10);* ***Frequent*** *(≥1/100 but <1/10);* ***Less frequent*** *(≥1/1000 but <1/100);* ***Rare*** *(≥1/10 000 but <1/1000);* ***Very rare*** *(<1/10 000);* ***Unknown frequency*** *(frequency that cannot be estimated based on available data)*

TABLE 2. PHE adverse reactions [25,46]

	Frequency	Adverse reactions
Psychiatric effects	Unknown frequency	Irritability
CNS effects	Unknown frequency	Headache, dizziness, insomnia, paresthesia, tremor
Cardiovascular	Unknown frequency	Palpitations, hypertensive crisis, bradycardia, AV block, ventricular extrasystoles, myocardial ischemia
Respiratory	Unknown frequency	Pulmonary edema, rales
GI	Unknown frequency	Nausea, diarrhea, vomiting
Dermatologic effects	Unknown frequency	Diaphoresis, pallor, piloerection, skin blanching, skin necrosis with extravasation

Frequency of adverse reactions is defined as the following convention: ***Very frequent*** *(≥1/10);* ***Frequent*** *(≥1/100 but <1/10);* ***Less frequent*** *(≥1/1000 but <1/100);* ***Rare*** *(≥1/10 000 but <1/1000);* ***Very rare*** *(<1/10 000);* ***Unknown frequency*** *(frequency that cannot be estimated based on available data).*

PHE administration is contraindicated in case of hypersensitivity, concurrent MAOI treatment, or if MAOIs were used within the past two weeks. Additionally, it should not be used during pregnancy or breastfeeding [47].

In patients with conditions such as hypertension, cardiovascular disease, diabetes, benign prostatic hyperplasia (BPH), thyroid disease, or phenylketonuria (as some oral products may contain phenylalanine), PHE should be administered with caution.

Drug interactions

Regarding interactions involving PSE and PHE, it is crucial to avoid their concurrent use with other sympathomimetic substances.

TABLE 3. PSE interactions [11,41]

Drug	Interaction
MAOIs	Synergistic sympathomimetic effect - risk of severe hypertension, hyperthermia, bradycardia, death – MAOI should be stopped two weeks before administering PSE
Other sympathomimetic drugs – phenylpropanolamine, phenylephrine, ephedrine, methylphenidate	Increased vasoconstricting effect, high risk of hypertensive crisis
Reversible MAO A inhibitors – linezolid, dopaminergic/ vasoconstrictor alkaloids	Increased vasoconstricting effect, high risk of hypertensive crisis
Inhalation agents for general anesthesia	Risk of perioperative acute severe hypertension – discontinuation of PSE 24 hours prior to the intervention is mandatory
Guanethidine, reserpine, methyldopa	Diminished PSE effect
Tricyclic antidepressants, digitalis glycosides, quinidine	Increased risk of hypertensive crisis/cardiac arrythmias
Antacids (aluminum hydroxide), proton pump inhibitors	Increased PSE absorption – increased effect
Terpenes, clobutinol, atropin-like agents, local anesthetics	Increased risk of seizures
Urine alkalinisation agents (e.g. sodium bicarbonate)	Increased reabsorption of PSE – increased risk of seizures, anxiety, insomnia, tachycardia, restlessness
Alcohol	Acute psychosis
Caffeine	Hyperthermia, increased blood sugar, increased insulin levels, increased C-peptide levels

TABLE 4. PHE interactions [48]

Drug	Interaction
MAOIs – isocarboxazid, phenelzine, tranylcypromine, rasagiline, selegiline	Risk of acute hypertension
Antibiotics - Linezolid	Risk of acute hypertension
Tricyclic antidepressants – amitriptyline, amoxapine, clomipramine, desipramine	Can increase or decrease effects of sympathomimetics by blocking reuptake of NE or blocking uptake of indirect sympathomimetics into the adrenergic neuron
Ergot derivatives – bromocriptine, cabergoline, dihydroergotamine, ergotamine	Risk of acute hypertension, vasospasm
General anesthetics – desflurane, isoflurane, ether, etomidate	Risk of hypertension, ventricular tachycardia
Ethanol	Ethanol increases and PHE decreases sedation
Caffeine	Caffeine and PHE both decrease sedation

Available products in Romania containing PSE/ PHE

TABLE 5. Available products in Romania containing PSE/PHE

Commercial name	Active ingredients	Pharmaceutical form	Dose
IBUPROPHEN + PSEUDOEPHEDRINE			
ADVIL RACEALA SI GRIPA	Ibuprofenum + Pseudoefedrinum	Soft capsules	200mg/30mg
IBUGRIP PLUS	Ibuprofenum + Pseudoefedrinum	Film-coated tablets	200mg/30mg
IBUPROFEN/PSEUDOEFEDRINA TEVA	Ibuprofenum + Pseudoefedrinum	Film-coated tablets	200mg/30mg
IBUSINUS	Ibuprofenum + Pseudoefedrinum	Film-coated tablets	200mg/30mg
IBUSTOP RACEALA SI GRIPA	Ibuprofenum + Pseudoefedrinum	Soft capsules	200mg/30mg
IBUVALEN FLU	Ibuprofenum + Pseudoefedrinum	Film-coated tablets	200mg/30mg
LAROFEN PLUS	Ibuprofenum + Pseudoefedrinum	Film-coated tablets	200mg/30mg
MODAFEN	Ibuprofenum + Pseudoefedrinum	Film-coated tablets	200mg/30mg
NUROFEN RACEALA SI GRIPA	Ibuprofenum + Pseudoefedrinum	Film-coated tablets	200mg/30mg
TEDOLFEN	Ibuprofenum + Pseudoefedrinum	Film-coated tablets	200mg/30mg
PADUDEN RACEALA SI GRIPA	Ibuprofenum + Pseudoefedrinum	Film-coated tablets	200 mg/30 mg
USPAFEN SINUS	Ibuprofenum + Pseudoefedrinum	Film-coated tablets	200mg/30mg
ACETAMINOPHEN + PSEUDOEPHEDRINE			
COLDACT SINUS	Paracetamolum + Pseudoephedrinum	Film-coated tablets	500mg/30 mg
PROSINUS	Paracetamolum + Pseudoephedrinum	Film-coated tablets	500mg/30mg
REVIGRIP SINUS	Paracetamolum + Pseudoephedrinum	Film-coated tablets	500mg/30mg
SANADOR SINUS	Paracetamolum + Pseudoephedrinum	Film-coated tablets	500mg/30mg
SINUFEN	Paracetamolum + Pseudoephedrinum	Film-coated tablets	500mg/30mg
RINOMOL PLUS	Paracetamolum + Chlorphenaminum + Pseudoephedrinum	Film-coated tablets	500mg/3mg/50mg
BIOFLU	Paracetamolum + Pseudoephedrinum + Dextromethorphanum	Soft capsules	250mg/30mg/10.51mg
DALERON COLD3	Paracetamolum + Pseudoephedrinum + Dextromethorphanum	Film-coated tablets	325mg/30mg/15mg
PHENYLEPHRINE			
FENILEFRINA HYPERICUM	Phenylephrinum	Pre-filled syringe	50мg/ml
FENILEFRINA AGUETTANT	Phenylephrinum	Solution for infusion	100µg/ml
FENEFRIN	Phenylephrinum	Ophtalmic solution	100mg/ml
BIORPHEN	Phenylephrinum	Solution for injection	10mg/ml
BIORPHEN	Phenylephrinum	Solution for injection/perfusion	0.1mg/ml
BIOFLU NAZAL	Phenylephrinum	Nasal spray	5mg/ml
BIOFLU NAZAL	Phenylephrinum	Nasal drops	2.5mg/ml
VIBROCIL	Phenylephrinum + Dimetindenum	Nasal spray/drops	2.5mg/0.25mg/ml
ACETAMINOPHEN + PHENYLEPHRINE			
CAFFETIN COLDMAX	Paracetamolum+Phenylephrinum	Powder for oral solution	1000mg/12,2mg

ANTINEVRALGIC SINUS	Paracetamolum + Cafeinum + Phenylephrinum	Film-coated tablets	500mg/25mg/5mg
ANTINEVRALGIC SINUS HOT DRINK	Paracetamolum + Phenylephrinum	Powder for oral solution	650mg/10mg
COLDFEXIN	Paracetamolum + Phenylephrinum	Powder for oral solution	500mg/12,2mg
COLDREX HONEY & LEMON	Paracetamolum + Acidum ascorbicum + Phenylephrinum	Powder for oral solution	750mg+60mg+10mg
COLDREX JUNIOR	Paracetamolum + Guaifenesinum + Phenylephrinum	Film-coated tablets	250mg/100mg/5mg
COLDREX JUNIOR HOTREM	Paracetamolum + Acidum ascorbicum + Phenylephrinum	Powder for oral solution	300mg+20mg+5mg
COLDREX LEMON	Paracetamolum + Acidum ascorbicum + Phenylephrinum	Powder for oral solution	750mg/60mg/10mg
COLDREX MAX RACEALA SI TUSE	Paracetamolum + Guaifenesinum + Phenylephrinum	Capsules	500mg/100mg/5mg
COLDREX MAXGRIP FRUCTE DE PADURE & MENTOL	Paracetamolum+Acidum Ascorbicum + Phenylephrinum	Powder for oral solution	1000mg+70mg+10mg
COLDREX SINUMAX RACEALA SI TUSE	Paracetamolum + Guaifenesinum + Phenylephrinum	Powder for oral solution	1000mg/200mg/12,2mg
COLDREX SINUS EXTRA	Paracetamolum + Chlorphenaminum + Phenylephrinum	Film-coated tablets	500mg/3mg/50mg
FERVEX RACEALA SI GRIPA PENTRU ADULTI	Paracetamolum + Acidum Ascorbicum + Phenyraminum	Granules for oral solution	500mg/200mg/25mg
PARASINUS PENTA	Paracetamolum + Acidum Ascorbicum + Phenylephrinum + Cafeinum + Terpini Hydras	Film-coated tablets	500mg/38mg/5mg/ 25mg/20mg
PROSINUS	Paracetamolum + Phenylephrinum	Powder for oral solution	600mg/12,2mg
REVIGRIP HOT LEMON	Paracetamolum + Guaifenesinum + Phenylephrinum	Powder for oral solution	500mg/200mg/10mg
TANTUMGRIP CU GUST DE LAMAIE SI MIERE	Paracetamolum + Phenylephrinum	Powder for oral solution	600mg/10mg
TANTUMGRIP CU GUST DE PORTOCALA	Paracetamolum + Phenylephrinum	Powder for oral solution	600mg/10mg
THERAFLU EXTRA RACEALA SI GRIPA	Paracetamolum + Pheniraminum + Phenylephrinum	Powder for oral solution	650mg/20mg/10mg
THERAFLU MAX RACEALA SI GRIPA	Paracetamolum + Acidum Ascorbicum + Phenylephrinum	Powder for oral solution	1000mg/70mg/10mg
THERAFLU MAX RACEALA SI TUSE	Paracetamolum + Phenylephrinum + Guaifenesinum	Powder for oral solution	1000mg/12,2mg/200mg
THERAFLU RACEALA SI TUSE	Paracetamolum + Phenylephrinum + Guaifenesinum	Capsules	500mg/6,1mg/100mg
THERAFLU SINUS RACEALA SI GRIPA	Paracetamolum + Phenylephrinum	Powder for oral solution	650mg/10mg
VICKS ANTIGRIP MAX	Paracetamolum + Phenylephrinum	Powder for oral solution	1000mg/12,2mg
GRIPPOSTAD ZI	Paracetamolum + Cafeinum + Phenylephrinum	Capsules	300mg/25mg/5mg

CONCLUSIONS

Pseudoephedrine's vasoconstrictive properties lead to speculation about its potential involvement in conditions associated with vasoconstriction, such as RCVS and PRES. However, there are many other risk factors that have been linked to these two conditions. Over the course of 16 years, only 33 cases worldwide have reported a link between PSE use and PRES/RCVS. Out of the 33 cases, only two lacked any risk factors for these conditions other than PSE use. Most experts leaned towards considering the association between PSE use and RCVS/PRES as more likely coincidental and found it unreasonable to label PSE as “unsafe”.

In december 2023 PRAC issued an official statement advising against the use of medicines containing PSE only in patients with uncontrolled severe hypertension or those with severe acute or chronic kidney disease. Additionally, PRAC recommends healthcare professionals to counsel patients to discontinue the use of such medicines promptly and seek medical assistance if they experience symptoms indicative of PRES or RCVS, such as sudden onset of severe headache, vomiting, confusion, seizures, or visual disturbances.

When it comes to oral PHE, expert consensus is uniformly unfavorable regarding its effectiveness. Both in vitro and in vivo clinical pharmacology data

indicate that neither the recommended doses nor higher doses of oral PHE demonstrate efficacy in alleviating symptoms of nasal congestion. Moreover, it has been demonstrated that the suggested 4-hour dosing interval is inadequate. This means that, in addition to lacking an effective dose, an appropriate dosing frequency for oral PHE is yet to be established.

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