



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

30 November 2023  
EMA/89241/2024  
Pharmacovigilance Risk Assessment Committee (PRAC)

## Assessment report

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Pseudoephedrine-containing medicinal products

Invented name: Aerinaze

INN: pseudoephedrine

Procedure number: EMEA/H/A-31/1526

Aerinaze EMEA/H/A-31/1526/C/000772/0047

Note:

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

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# 1. Information on the procedure

New evidence related to posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) was identified by PRAC during the periodic safety update report single assessment (PSUSA) procedure for ibuprofen/pseudoephedrine medicines (PSUSA/00001711/202207) concluded in February 2023. PRES and RCVS are considered serious risks associated with major and life-threatening complications like strokes. After an assessment of the data in the PSUSA, the observed reactions of PRES and RCVS were considered as related to pseudoephedrine use in view of the reported cases (spontaneous and literature case reports) including a compatible and suggestive time to onset (TTO), the biological plausibility and the lack of alternative aetiologies observed for some patients without any risk factors of PRES or RCVS. The known safety profile of pseudoephedrine includes serious adverse drug reactions such as strokes (haemorrhagic or ischaemic), myocardial infarction (MI) or ischaemic cardiomyopathies, hypertensive crisis or elevation in blood pressure. While in some EU countries, PRES and RCVS are already labelled for some pseudoephedrine-containing products, the set of data from the PSUSA procedure enabled to have an up-to-date overview of the risks of PRES and RCVS associated with the use of pseudoephedrine-containing medicinal products. Overall, the French national competent authority was of the view that the accumulation of severe risks of ischaemic nature and the whole safety profile of pseudoephedrine-containing medicinal products questioned the benefit-risk balance of these medicines, in particular in view of the approved indications (symptomatic relief of nasal or sinus congestion caused by common cold, flu, sinusitis, allergic rhinosinusitis, vasomotor rhinitis and aerotitis [otitis barotrauma]).

On 3 February 2023, the French national competent authority therefore triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of pseudoephedrine-containing products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

## 2. Scientific discussion

### 2.1. Introduction

Pseudoephedrine is an alpha-adrenergic receptor agonist. Its mechanism of action as decongestant is based on the constriction of dilated arterioles of nasal mucosa and reduction of blood flow, which reduces rhinorrhoea and nasal congestion. Following the oral administration of a single dose of pseudoephedrine, nasal decongestion occurs within 30 minutes and persists for 4 to 6 hours.

Pseudoephedrine-containing medicinal products are used for the symptomatic relief of nasal or sinus congestion caused by common cold, flu, sinusitis, allergic rhinosinusitis, vasomotor rhinitis and aerotitis (otitis barotrauma). In many authorised pseudoephedrine-containing medicinal products available in the EU, pseudoephedrine is combined with other active substances, such as antihistamines, analgesics, and/or antitussives. These combinations act as a multi-symptom relief in respiratory conditions. Pseudoephedrine-containing medicinal products have been approved for several decades as prescription-only medicines (POM) and over the counter (OTC) medicines.

Pseudoephedrine-containing medicinal products are available in most of the EU Member States, the majority having been authorised nationally and one through the centralised procedure: Aerinaze (desloratadine 2.5 mg/pseudoephedrine 120 mg). Pseudoephedrine-containing medicinal products are widely used, with a reported exposure of millions of patients per year.

The efficacy of pseudoephedrine-containing medicinal products in the authorised indications is considered established in short-term reduction of nasal congestion. In terms of safety, pseudoephedrine-containing medicines are known to be associated with cardiovascular risks such as hypertension, arrhythmias, cardiac failure, ischaemic risks (transient ischemic attack, MI, cerebrovascular accident, ischemic colitis and ischemic optic neuropathy) or haemorrhagic stroke. These adverse events are labelled in the product information at varying extent. Different levels of restrictions and warnings are included in the product information of some pseudoephedrine-medicinal products to reduce these risks. The extent of the information related to cardiovascular and cerebrovascular risks differs across individual medicinal products.

As part of the PSUSA procedure for pseudoephedrine in combination with ibuprofen (PSUSA/00001711/202207) concluded in February 2023, new safety data related with ischaemic cerebrovascular adverse drug reactions, particularly spontaneous cases of PRES and RCVS, were identified by PRAC in the EudraVigilance data analysis system (EVDAS) and in the literature. These ischaemic events contributed to an accumulation of severe risks of ischaemic nature observed in association with pseudoephedrine-containing products. Therefore, it was considered that a thorough assessment was needed to assess the impact of these concerns on the benefit-risk balance of pseudoephedrine-containing products. A referral procedure was initiated accordingly.

As part of this review, the PRAC requested the marketing authorisation holders (MAHs) of pseudoephedrine-containing medicinal products to perform a literature review focused on publications regarding serious ischaemic neurological disorders (with a focus on PRES/RCVS events) after administration of pseudoephedrine and propose risk minimisation measures to prevent or mitigate the risks of cerebrovascular events and other known ischaemic events. The PRAC also considered an EudraVigilance (EV) analysis performed by EMA and consulted experts in the context of an ad-hoc expert group meeting, to gather further information and their views on the matter. A third-party submission was also received as part of this procedure. A summary of the most relevant information is included below.

## **2.2. Data on safety**

### **2.2.1. Posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome**

**Posterior reversible encephalopathy syndrome (PRES)** is a clinical and radiological entity, firstly described in 1996. The neuroimaging finding characteristic of PRES is a bilateral reversible vasogenic oedema of the subcortical white matter in the parieto-occipital regions. Neuroimaging examinations, such as contrast computed tomography (CT) and magnetic resonance imaging (MRI), especially T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences, are essential for PRES diagnosis. Clinical manifestations include a wide variety of acute or subacute neurological symptoms, such as headache, mental status alteration, seizures, visual disturbances and focal neurologic deficits, with an acute or sub-acute onset of the symptoms (hours to days). PRES is usually reversible; the symptoms can develop within several hours or days and resolve within several days or weeks following blood pressure reduction and retraction of the causative drugs, however cases of irreversible or fatal PRES have been also reported in intensive care unit (ICU) patients with comorbidities. In a retrospective cohort study performed by Legriél et al. (2012), out of 70 patients with PRES, 11 patients (16%) died, 26 (37%) had marked functional impairments, and 33 (56%) had a good recovery. Early recognition of PRES and interventions to address the underlying cause, including blood pressure reduction, antiepileptics, or sedation, stopping or switching drugs, correction of electrolyte disturbances with hydration, are key to achieve favourable clinical outcomes.

PRES was reported in all age groups (from 2 to 90 years), although it most commonly occurs in young or middle-aged adults, with a predominance in females (even after exclusion of patients with pre-eclampsia). Incidence in the general population is unknown. In selected populations, the incidence has been reported to be 0.8% among patients with end-stage renal disease, approximately 0.7% among those with systemic lupus erythematosus (SLE), 0.5% among those who have undergone solid-organ transplantation, and from 20.0% to 98.0% among those with preeclampsia or eclampsia (Geocadin, 2023).

The exact pathophysiology of PRES is not clearly elucidated. A possible hypothesis is that severe hypertension is a possible disruptor of the brain autoregulation system, resulting in endothelial oedema or injury. An alternative hypothesis is that endothelial dysfunction is caused by circulating endogenous or exogenous toxins.

The most common recognised risk factor of PRES is an abrupt increase in blood pressure. Medical conditions, diseases and drugs causing fluctuations in blood pressure can be also considered as risk factors for PRES. In the literature, the reported risk factors include renal disease, autoimmune disorders (e.g. SLE, Sjogren's disease, scleroderma), infections/sepsis, pre-eclampsia, immunosuppressive and chemotherapeutic drugs (e.g. cyclosporin A, tacrolimus, methotrexate, vincristine), stimulant drugs (including pseudoephedrine), steroids, dialysis, transfusion, surgery, anaemia, or hypomagnesemia (Ando, 2022; Gewirtz, 2021; Hinduja, 2020; Legriél, 2012).

The differential diagnosis of PRES includes cerebral infarction, especially posterior-circulation or watershed strokes, central nervous system (CNS) infections, demyelinating diseases, brain cancers, dural venous sinus thrombosis, CNS vasculitis, toxic encephalopathies, and mitochondrial disorders. Some cerebrovascular dysregulation syndromes, particularly RCVS, in which there are irregular segments of cerebral vessel constriction, may overlap with PRES. An assessment of patient's history, cerebral imaging, blood and urine samples, and cerebrospinal fluid studies - particularly in a patient with extreme and abrupt hypertension or in the presence of one of the known drug triggers - helps to refine the differential diagnosis (Geocadin, 2023).

**Reversible cerebral vasoconstriction syndrome (RCVS)** is a medical condition in which there is multifocal arterial constriction and dilation in the cerebral vasculature, and that may be associated with non-aneurysmal subarachnoid haemorrhage. This condition was previously also known as "benign cerebral vasculitis", "Call or Call-Felmming syndrome" and "migrainous vasospasm" (Nesheiwat, 2023).

The clinical manifestation of RCVS is characterised by thunderclap headache (severe pain peaking in seconds) as first symptom that typically recur for 1-2 weeks. This typical headache is bilateral, with posterior onset followed by diffuse pain frequently accompanied by nausea, vomiting, photophobia and phonophobia. In contrast to the headache associated with ruptured aneurysm, the severe pain associated with RCVS is of short duration (1-3 hours). An average of four attacks in the time span of 1-4 weeks is reported in the literature (Ducros, 2012). Patients typically report at least one trigger such as sexual activity (usually just before or at orgasm), straining during defecation, stressful or emotional situations, physical exertion, coughing, etc. Transient focal deficits are present in slightly more than 10% of patients, lasting from 1 minute to 4 hours, and are most frequently visual. However sensory, dysphasic, or motor deficits can also occur. In most patients, headaches and angiographic abnormalities resolve within days or weeks. Ischaemic and haemorrhagic stroke are the major complications of RCVS. Data available from the literature suggest that less than 5% of patients develop life-threatening forms with several strokes and uncontrolled massive brain oedema (Ducros, 2012).

Diagnosis of RCVS is based on direct (transfemoral) or indirect (CT/MRI) cerebral angiography showing segmental narrowing and dilatation (string of beads) of one or more arteries. The basilar artery, the

carotid siphon, or the external carotid artery can be affected. The narrowing of the arteries is temporary. A repeated angiogram after a few days might show resolution of the constriction of some vessels, with eventual new constrictions often affecting more proximal vessels.

The true incidence of RCVS is not known, because prompt and accurate diagnosis remains challenging. However, clinical experience suggests that RCVS is relatively common (Nesheiwat, 2023). RCVS has been reported to occur in the age groups from 10 to 76 years, with a peak occurrence at around 42 years. It is a rare condition with a reported incidence of 4.62 per million (Patel, 2020) showing clear female predominance (7.20 females vs 1.91 males). RCVS can be either idiopathic or secondary to various factors. A trigger for RCVS is identified in approximately 25% to 60% of cases. There are various possible aetiologies. The most common recognised causes of RCVS are related to the use of vasoactive substances and post-partum state.

The exact pathophysiology of RCVS is unclear. The proposed pathophysiological models suggest a combination of predisposing factors (genetic, gender) and precipitating factors (vasoactive substances, post-partum, external triggers) causing endothelial dysfunction, sympathetic over-reactivity and oxidative stress resulting in blood-brain barrier disruption and cerebral vascular tone dysregulation. A non-exhaustive list of identified precipitants of RCVS includes post-partum state (with or without vasoactive substances, with or without eclampsia or pre-eclampsia), vasoactive drugs (antidepressants – selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), alpha-sympathomimetics – phenylpropanolamine, pseudoephedrine, ephedrine, norepinephrine, triptans, ergot alkaloid derivatives, etc.), catecholamine-secreting tumours, immunosuppressants or blood products, migraine, hypercalcaemia, porphyria, head trauma, phenytoin intoxication (Ducros, 2012; Chen, 2022; Patel, 2020; Pilato, 2020; Nesheiwat, 2023).

PRES and RCVS share precipitating factors, clinical and radiological features, and can co-exist, suggesting a common pathophysiological mechanism related to reversible dysregulation of cerebral vasculature, endothelial dysfunction, and breakdown of the blood-brain barrier (Jeanneret, 2022). Table 1 presents the comparison of the clinical and radiological characteristics of PRES and RCVS.

**Table 1 - Comparison of clinical and radiological characteristics in PRES and RCVS**

	<b>PRES</b>	<b>RCVS</b>
<b>Clinical features</b>		
Associated clinical conditions	Immunosuppression, malignancy, pre-eclampsia, renal failure, dialysis, autoimmune disorders, infection, sepsis, hypertension, transplantation, chemotherapeutic medications, idiopathic	Pregnancy and puerperium, exposure to vasoactive drugs and blood products, head trauma, neurosurgical procedures, idiopathic
Headache	Moderate/severe	Thunderclap type
Seizures	Common	Uncommon
Encephalopathy	Common	Uncommon
Visual impairment	Common	Uncommon
Focal neurological deficits	Uncommon	Common in ischemic and haemorrhagic lesions
<b>Radiological features</b>		
Lesions distribution	Symmetric	Asymmetric

Oedema distribution	Common: parieto-occipital pattern, holohemispheric watershed pattern, superior frontal sulcus pattern Uncommon: partial or asymmetric expression of above primary patterns	Uncommon: PRES-like
Ischemic lesion	Uncommon	Common
Haemorrhage lesion	Common: punctate type Uncommon: subarachnoid haemorrhage, intracerebral haemorrhage	Common: subarachnoid haemorrhage, intracerebral haemorrhage
Vasoconstriction	Uncommon	Common: string-of-beads, distal vascular pruning

Table adapted from Pilato, 2020

### 2.2.2. EudraVigilance case reports analysis for PRES and RCVS

The EMA performed an analysis of EV data for cases of ‘central nervous system vascular disorders’ and ‘encephalopathies’ (high level group term [HLGT]) with pseudoephedrine-containing medicinal products reported as suspect, interacting or concomitant. All report types (spontaneous, report from studies, other, not available to sender, unknown) were included in the analysis. Overall, 872 cases were retrieved, 101 of which (11.6%) were fatal. The majority of the cases (713 reports, 81.8 %) were reported from the United States (US) and 98 reports (11.2 %) were from Europe. Median age was 52 years and there was a female predominance (62%). Pseudoephedrine-containing medicinal products were considered suspect/interacting in 36.1% of the cases. Pseudoephedrine single ingredient was the most frequently reported. A medical history was reported in 76% of cases. Hypertension was the most frequent history term, with 241 cases (27.6%). A high level of polypharmacy was observed, with an average of 14.2 drugs (SD=14.3) per case and a median of 10 drugs (range: 1-128).

Two disproportionality analyses were conducted. The first analysis aimed at contextualising cases of PRES/RCVS with pseudoephedrine-containing medicinal products considering other drugs associated with these terms. The second aimed at contextualising cases of PRES/RCVS with pseudoephedrine single ingredient considering other reactions reported for pseudoephedrine. In accordance with the guidance entitled “Screening for adverse reactions in EudraVigilance”, the following thresholds were used to define a signal of disproportionate reporting (SDR): lower bound of the 95% confidence interval of the reporting odds ratio (ROR (-)) > 1; number of individual cases ≥ 5. A SDR was observed for pseudoephedrine single ingredient and ‘reversible cerebral vasoconstriction syndrome’. There were other drug-event combinations with elevated ROR (-), but the case count threshold for a SDR was not met.

Cases of interest were defined as cases from two eligible HLGT groups with pseudoephedrine use described in case narratives, when patients experienced symptoms suggestive of RCVS or PRES such as headache (sudden, thunderclap headache), nausea, vomiting, visual disturbances, confusion according to the clinical presentation and medical course of PRES and RCVS described in the UpToDate website. Available data on concomitant conditions, neuroimaging and TTO were considered in order to assess causality to pseudoephedrine.

Among the retrieved cases (872), 33 cases with coded PRES or RCVS were identified (29 cases spontaneous and 4 reported from studies), 17 of them assessed as probably or possibly related to pseudoephedrine. Additional 15 cases assessed as probably or possibly related to pseudoephedrine were identified in the dataset retrieved by HLGT analysis. In total, thirty-two (32) cases of PRES and



RCVS were assessed as probably or possibly related to pseudoephedrine in the EV analysis. Six (6) cases were related to PRES (2 cases as probably; 4 as possibly) and 26 cases to RCVS (16 cases as 'possibly', 10 cases as 'probably'). All cases were serious, hospitalisation was coded in 25 cases and in 7 cases the hospitalisation was described in narratives or the stated imaginings indicate hospitalisations. None of the 32 cases was fatal. Duration of treatment was coded or described in narratives in most of cases and ranged from 1 hour to 1 week (without cases with stated long-term use of pseudoephedrine). Four (4) cases of RCVS (described as 15-day administration, 37-day administration, regular long-term use, habit in consumption) and 1 case of PRES (described as long-standing prescription) presented long-term use of pseudoephedrine. When known, TTO ranged from one hour to 10 days. The indication was known in 23 from 32 cases assessed as PRES/RCVS probably or possibly related to pseudoephedrine. In the majority of cases, the indication was related to upper respiratory symptoms of cold/flu. Allergy was stated in 4 cases only. Pseudoephedrine dosage and frequency of administration were vaguely described in many cases (for example, several days before developing symptoms in the indicated dosage). In some cases, several pseudoephedrine-containing products were used simultaneously and the cumulative dosage from several different products was unclear. There was no available data confirming the association between the number of doses of pseudoephedrine and the level of risk of PRES/RCVS. Therefore, no potential dose-response relation was established for these adverse events.

Risk factors related to RCVS and PRES were present in most of the cases (27/32): concomitant use of SSRI, triptans, hormonal contraception, hormone replacement therapy (HRT), chlorphenamine and other sympathomimetics (oxymetazoline, naphazoline, adrenaline), migraine, chemotherapy in recent history, hypertension, patent foramen ovale and atrial septal aneurysmal, post-partum condition, renal disorder, autoimmune disease, sepsis, history of brain oedema, dyslipidaemia, high alcohol consumption. Moreover, in 3 cases the only potential risk factor identified was the observed long-term use of pseudoephedrine. Two (2) additional cases reporting possible overuse/prolonged use of pseudoephedrine were confounded by other conditions considered risk factors (recent chemotherapy treatment, hypertension, renal disease and high alcohol consumption) were identified. In 5 cases, risk factors were not present. The outcome for these 5 patients was that 3 of them fully recovered and 2 recovered with sequelae (right hemibody deficit and hemiparesis; cephalgia). The outcomes of cases with identified risk factors were "recovered/resolved" or "recovering/resolving" at the time of reporting in 16 cases, "recovered/resolved with sequelae" in 3 cases (persistence of balance disorders, paresis of the left hemibody; mild spasticity in left leg; attentional/concentration troubles, tendency to depressed mood, increased amount of sleep, migraine auras without headaches) and "unknown" outcome in 7 cases (one unknown outcome due to missing case narrative in EV). One case was reported with an outcome stated as "not recovered/not resolved".

## **2.2.3. Published literature**

### **2.2.3.1. PRES and RCVS**

The MAHs provided case reports from the literature describing PRES/RCVS observed after administration of pseudoephedrine. In total, 27 literature reports were identified, most of them (25/27) describing cases retrieved in the EV analysis (see section 2.2.2.). Two (2) additional cases of RCVS were retrieved (Jacoby, 2015 and Dong, 2016) and further assessed. In the first case reported by Jacoby et al. (2015), an history of use of cocaine and marijuana in the previous 5 days, presence in a high-altitude location and thunderclap headaches were reported in the medical history of the patient. These were considered as risk factors for the observed RCVS. The TTO was within hours after pseudoephedrine use, with complete resolution a month later. The case was assessed as possibly related to pseudoephedrine. In the publication by Dong et al, (2016) a case of RCVS was described in a



female patient after a 3-day treatment with pseudoephedrine for allergic rhinitis. The medical history included prior headaches. The article does not provide any information on possible risk factors and on the outcome. This case of RCVS was assessed as possibly related to pseudoephedrine.

In addition to the case reports described in the literature, the currently postulated pathophysiological mechanisms recognise vasoactive agents as known triggers of PRES and RCVS. All MAHs provided additional literature articles describing PRES/RCVS in general as well as when described in relation with pseudoephedrine use. More than 50 additional literature articles were identified. Several literature publications assessed in the present review (Kopel, 2021; Ducros, 2007/2012; Patel, 2021; Bernstein, 2006; Miller, 2015; Goddeau, 2013; Erhart, 2023; UpToDate -website) identify pseudoephedrine specifically as a trigger of PRES and RCVS.

### **2.2.3.2. Ischaemic events**

Concerning other ischaemic events, multiple articles (Rosen, 1981; Wright, 1994; Derreza, 1997; Grzesk, 2004; Pederson, 2001; Wiener, 1990; Manini, 2005) describe an association of angina pectoris and/or myocardial ischemia with the use of pseudoephedrine. The article by Kendirli et al. (2006) describe an association of haemorrhagic stroke with pseudoephedrine. The article by Profice et al. (2006) describe transient ischemic attack (TIA) after administration of pseudoephedrine. The article of Eccles et al. (2007) states that there is no evidence that pseudoephedrine has adverse effects on the cardiovascular system in normotensive subjects and pseudoephedrine is reported to be safe in patients with controlled hypertension, although the authors reported scant clinical data on the topic.

A follow-up study of over 100,000 persons below the age 65 years who filled a total of 243,286 prescriptions for pseudoephedrine, indicated that there were no hospitalisations among users that could be attributed to the drug. There were no admissions within 15 days of filling a prescription for pseudoephedrine for cerebral haemorrhage, thrombotic stroke, or hypertensive crisis. There were a small number of hospitalisations for myocardial infarction, seizures and neuropsychiatric disorders, but the rate of such admissions among the pseudoephedrine users was close to the expected rate in the general population (Porta, 1986).

A stroke registry study conducted since 1988 found that 22 of 2,500 consecutive stroke patients in a neurological reference centre had a stroke after using an OTC cough and cold sympathomimetic drugs (within 24 hours before the stroke onset). These were implicated in 2.5% of the patients with intracerebral haemorrhage and in 8.1% of the cases with non-aneurysmal subarachnoid haemorrhage (SAH). The authors reported that although most cases were related to phenylpropanolamine, stroke could also occur after use of other sympathomimetics, particularly pseudoephedrine. In 4 cases, haemorrhagic stroke was associated with pseudoephedrine (dose 60 to 300 mg). Stroke occurred after recommended doses of pseudoephedrine (60 mg) in 50% of patients. One patient was given a single regular dose, 2 received a single but excessive dose, and 1 took recommended doses of pseudoephedrine daily for 1 week (Cantu, 2003).

Caravati et al., (2005) describe a population-based study of pseudoephedrine adverse reactions in a retrospective study using one medical plan's prescription and hospital admission database. Patients were evaluated for evidence of hospitalisation possibly related to pseudoephedrine use within 15 days of filling a prescription for the drug. Patients between 20 and 64 years of age filled more than 160,000 prescriptions, and 6 cases of MI were identified. The rate of MI for the pseudoephedrine users was low (1.2 to 6.7 per 100,000 person-days at risk) but slightly higher than expected for the population in general (0.9 to 5.0 per 100,000 person-days at risk). The study did not identify cases of stroke or hypertensive crisis.

Reports of MI and ischaemic stroke (IS) associated with nasal decongestants (oral and intranasal) registered in the French Pharmacovigilance Database from 1985 to 1 June 2019 were also studied by Lafaurie et al., (2020). Twenty-one MI events were reported. More than 70% had at least 1 cardiovascular risk factor (4 men > 50 years, 1 woman > 60 years, 4 familial histories of MI, 3 dyslipidaemias, 3 tobacco smokers, 2 arterial hypertensions, 2 diabetes, 2 overweight patients). The most frequently suspected drugs were pseudoephedrine (n=14, 66.7%) followed by oxymetazoline (n=4, 19.0%). Fifty-two IS events were reported. Cardiovascular risk factors were found in 32 reports (61.5%) (10 men > 50 years, 9 women > 60 years, 10 arterial hypertensions, 8 dyslipidaemias, 8 tobacco smokers, 5 migraines, 5 overweight patients, 1 diabetes, 1 atrial fibrillation). The most suspected drugs were pseudoephedrine (n=27, 51.9%) and naphazoline (n=12, 23.1%). Other suspected drugs were reported in 28.8% (n=15), mainly nonsteroidal anti-inflammatory drugs (NSAIDs) (n = 4) or corticosteroids (n = 4). Two patients died. The authors conclude that, despite the limitation of a pharmacovigilance survey, the study highlighted the seriousness of these adverse drug reactions and the importance of a careful prescription of the nasal decongestants, especially in at-risk patients.

Laccourreye et al. (2015) conducted a review of the literature to determine the benefit, limitations and dangers of ephedrine and pseudoephedrine use in rhinology. The authors report that pseudoephedrine considerably increases blood pressure and vasospasm. This effect, which on average lasts 5 to 6 times as long as that of adrenaline, may induce hypertension episodes, myocardial infarction, stroke and various neurological symptoms. The various cardiovascular adverse effects may occur with both oral and nasal administration and after a single dose or prolonged (5 days) treatment, without dose-effect and independently of vascular status and age. The article highlighted a French study published in 2003 by Olivier et al. which analysed adverse events related to nasal decongestant vasoconstrictors reported to regional pharmacovigilance centres by healthcare professionals (HCPs) between the market launch of nasal decongestants in France and 2001. The study noted 22 episodes of arterial hypertension, 15 of convulsion and 4 cases of stroke after oral intake of medication containing pseudoephedrine and 1 episode of arterial hypertension and 1 case of stroke after nasal intake of ephedrine.

More recently, Grimaldi-Bensouda et al. (2021) aimed to assess the risk of stroke and MI associated with the use of decongestants. The authors conducted a nested case-crossover study of patients with incident stroke and MI identified in France between 2013 and 2016 in two systematic disease registries (data from 200 clinical centres in France). Decongestant use in the three weeks preceding the event was assessed. Conditional logistic multivariable models were used to estimate the odds of incident MI and stroke, also accounting for transient risk factors and comparing week 1 (index at-risk time window, immediately preceding the event) to week 3 (reference). In total, 1,394 patients with MI and 1403 patients with stroke, mainly 70 years old or younger, were interviewed, including 3.2% who used decongestants during the three weeks prior to the event. A secondary analysis yielded similar results for individual events (MI/stroke). No increased risk of MI or stroke was observed in patients of 70 years of age and younger without previous MI or stroke who used decongestants. However, the study had several limitations as the paucity of data for patients over 70 years of age due to the local restriction of the use of decongestants in this population and patients who died rapidly after their event were not identified or interviewed in time.

#### **2.2.4. Discussion on safety**

Pseudoephedrine-containing medicines are known to be associated with cardiovascular risks such as hypertension, arrhythmias and cardiac failure, ischaemic risks (transient ischemic attack, MI, cerebrovascular accident, ischemic colitis and ischemic optic neuropathy) or haemorrhagic stroke. Different levels of restrictions and warnings are already included in the product information of

pseudoephedrine-containing products. It is noted that the extent of the information related to these risks differs across individual products. The MAHs are reminded to keep their product information in line with the current scientific knowledge regarding cardiovascular and cerebrovascular risks. Risk of abuse is another well-known risk of pseudoephedrine-containing products. Likewise, while their characteristics and extent differ across individual Member States, there are currently risk minimisation measures in place in some EU Member States to address this risk.

Concerning the new safety concerns of PRES/RCVS that triggered this referral procedure, a total of 34 cases were identified in EV and in the literature (32 and 2 cases, respectively). Overall, the number of case reports of PRES or RCVS identified as related to pseudoephedrine (n=34) was not considered high when comparing with the high patient exposure to pseudoephedrine. However, all cases were serious and assessed as probably or possibly related to pseudoephedrine, including 6 cases related to PRES syndrome (2 as probably related, 4 as possibly related) and 28 cases to RCVS syndrome (18 as possibly related, 10 as probably related). None of the cases assessed as probably or possibly related to administered pseudoephedrine was fatal, but all cases were classified as serious and associated with hospitalisation. Out of 34 cases, 20 of them reported as outcome "resolved" or "resolving", in 8 cases the outcome was "unknown" and 5 cases reported sequelae. Despite not observed in the cases reviewed, cases of irreversible or fatal PRES have been reported. Additionally, life-threatening forms of RCVS with several strokes and uncontrolled massive brain oedema have been reported. Therefore, PRES and RCVS are considered serious conditions, which should have a prompt diagnosis and treatment.

Pseudoephedrine is described in the literature as a precipitant factor for the development of PRES and RCVS along with other vasoactive agents. Clinical data indicate that pseudoephedrine can cause a dose-dependent increase in blood pressure, which is a recognised risk factor for cardiovascular and cerebrovascular complications including PRES and RCVS. Additionally, the relationship between plasma or serum concentrations of pseudoephedrine and blood pressure is documented in the literature. The pseudoephedrine peak appeared to be associated with a significant increase in systolic blood pressure. Thus, it is assumed that the extension of pseudoephedrine's half-life, even at normal therapeutic doses, would cause regional vasoconstriction and an increase in intracranial blood pressure. Furthermore, as described above, cardiac and vascular disorders are known risks of pseudoephedrine-containing medicines. These risks partially overlap with the described pathophysiological mechanism of PRES/RCVS development.

Taken together, the reported cases and the literature evidence which describes pseudoephedrine as a trigger of RCVS and PRES lead to the conclusion that the causal relationship between pseudoephedrine and PRES and RCVS is at least reasonably possible. Based on the number of cases observed in the post-marketing setting and using the methodology described in the 'Guideline on SmPC' by EC (September 2009, Revision 2), the attributable frequency is considered 'not known'.

The majority of patients in the case reports reviewed had some risk factors for developing PRES or RCVS (28/34 cases). The reported risk factors included hypertension, renal disease, sepsis, autoimmune disease, acute kidney injury, concomitant use of oral contraception, SSRI and vasoactive medicines, history of migraine, post-partum state and hormonal replacement therapy.

There is an established link between severe hypertension and the risk of PRES and RCVS. Pseudoephedrine has also known hypertensive effects as described above. Within the assessment of the cases of interest, 6 cases were reported with cardiovascular disease in the medical history of the patients, particularly hypertension. Patients with severe hypertension or uncontrolled hypertension treated with pseudoephedrine-containing medicinal products are therefore considered to be at an increased risk to develop PRES and RCVS. Additionally, in multiple articles, impaired kidney function (renal diseases, acute kidney injury, renal failure, end-stage renal disease and renal impairment) is

reported as a significant risk factor for PRES. Both acute and chronic kidney disease are reported to be associated with RCVS (Jorge, 2007; Ganesh, 2017). Pseudoephedrine is primarily excreted by the kidneys. Renal impairment is known to increase plasma levels of pseudoephedrine and should not be used by those with severe renal impairment (Zerbib, 2022; Lioger, 2016; Ebbo, 2010; Hinduja A, 2020). Within the assessment of EV cases of interest, 3 cases reported acute and chronic renal disease in the medical history of the patients. As conclusion, patients with kidney disease/renal failure are considered to be at an increased risk of PRES and RCVS when taking pseudoephedrine-medicinal products.

Lastly, from the data review, there was no pattern indicating a difference in the risk of any particular fixed-dose combination of pseudoephedrine. Additionally, no data confirming a dose-response was noted. Therefore, no potential dose-response relation was established.

### **2.3. Data on efficacy**

The efficacy of pseudoephedrine-containing medicinal products in the authorised indications was considered well-established and not questioned in this procedure. Efficacy was demonstrated in multiple studies and no new efficacy data were identified during this review.

### **2.4. Expert consultation and Stakeholder input**

#### **2.4.1. Expert consultation**

The PRAC consulted an *ad-hoc* expert group (AHEG), composed of allergologists, otorhinolaryngologists, general practitioners and a patient representative. The consulted experts provided advice on the place of pseudoephedrine in the management of nasal/sinus congestion in common cold/flu and allergic rhinitis, on the magnitude and nature of the reported risks (PRES and RCVS), and on the impact in the clinical practice if the use of pseudoephedrine products would be partially or fully restricted.

The experts stated that the use of pseudoephedrine is mostly in common cold/upper respiratory tract infections as these are self-limiting diseases and the short-term use addresses the congestive symptoms and increases the quality of life in these conditions. The medicine is used in many age groups, but some experts stated that they recommend it primarily in children and younger patients without cardiovascular risk factors or other comorbidities and for short duration. From the experts' experience, the use of pseudoephedrine in allergic rhinitis is limited due to the availability of antihistamines, intranasal corticosteroids and immunotherapy, which were referred by the experts as preferred therapeutic options. Some experts also mentioned that allergic rhinitis symptoms do not require usually nasal decongestion, but the use of pseudoephedrine could be relevant as rescue therapy for short term only in patients with severe nasal congestion that cannot be managed otherwise or in case of acute exacerbations. One expert stated that there would be no use of oral pseudoephedrine in allergic rhinitis in their Member State due to its cardiovascular risks. It was further noted that allergic rhinitis is usually of longer duration than a common cold (can be 8 weeks or longer) which makes a short-term treatment of limited relevance.

The differences in national treatment guidelines for upper respiratory tract infections and allergic rhinitis and differing prescribing practices in these conditions in the different Member States were highlighted by the experts.

The experts agreed that pseudoephedrine is a symptomatic treatment without disease modifying effects. Whilst nasal congestion was considered a relevant symptom highly impacting the quality of life of patients, according to the experts' knowledge, there is no evidence of pseudoephedrine preventing

complications from common cold or allergic rhinitis. Complications from common cold or allergic rhinitis were considered by the experts to be connected rather to the general/immune status of the patient and the type of virus or bacteria.

The experts considered the risk of PRES and RCVS to be low and that PRES and RCVS could also be caused by other factors, including respiratory viruses. Some experts highlighted that they are more concerned about the known cardiovascular risks associated with pseudoephedrine in combination with the use of pseudoephedrine in the over the counter (OTC) setting in patients with hypertension or history of cardiovascular disease.

Considering that the majority of the allergology experts do not or only rarely prescribe pseudoephedrine for allergic rhinitis, they felt that these new risks would not influence their prescribing patterns. For some experts, including general practitioners, prescribing pseudoephedrine would need to be considered with an evaluation of the risk factors (e.g., age, cardiovascular conditions, nervous system conditions, thyroid dysfunction). For these patients, the prescription would be accompanied by warnings to the patients and recommendations to reduce the duration of use and to not associate with other medicines containing similar substances. To note, one expert reported to not prescribe routinely pseudoephedrine due to its cardiovascular risk as well as due to the risks of misuse and abuse.

Concerning misuse and abuse, some experts commented on these concerns for OTC medicines and, in particular, how clinical guidelines recommend that pseudoephedrine should only be used for short term treatment of nasal congestion. In reality it is also used as self-medication by patients with allergic rhinitis awaiting a consultation with a specialist.

Although most of the experts do not use pseudoephedrine in the treatment of allergic rhinitis and only some prescribe it for nasal congestion, most of the experts expressed support in keeping the status of the product as OTC for different reasons: several highlighted an increased burden to the national healthcare systems if the products were required to be prescribed by a physician, whereas only some considered suitable that the pharmacist takes the responsibility to ask appropriate questions via a questionnaire. This questionnaire was briefly discussed and there were concerns expressed regarding the suitability of long checks and ensuring patient privacy in busy pharmacies. In addition, if pseudoephedrine products were to be withdrawn from the market, experts claimed that this would impact the patient accessibility to a reported effective treatment for symptomatic relief with impact on patient quality of life. Additionally, the number of effective decongestants in the market for those patients where pseudoephedrine is indicated would be limited. To note, one expert stated that there is no medical need for use of pseudoephedrine and therefore withdrawal from the market would not have an impact for the expert.

Furthermore, while some experts considered that changes to the product information and additional risk minimisation measures would not mitigate the risks and that the withdrawal of pseudoephedrine products would cause no loss in the system, others insisted that actions should be taken to prevent the misuse and abuse of pseudoephedrine medicines beyond short term treatment, including making the patient leaflet more user-friendly, having a form of register purchase, providing physicians and pharmacists with more information on the risks to increase awareness, providing a patient card, decreasing the pack size and limiting the number of packs that one person could buy. Most of the experts also agreed that, although OTC status may still be appropriate, pharmacies should only offer the product behind the counter. These measures were also supported overall by the patient representative.

## **2.4.2. Stakeholder input**

The PRAC received, during the assessment of this procedure, a report from the Pharmaceutical Group of the European Union (PGEU). The report highlighted the level of awareness of pharmacists regarding the safety profile of pseudoephedrine-containing medicines and included a number of proposals for risk minimisation measures, some of which were considered by PRAC (pop-up alerts in the pharmacy software; training and awareness campaigns directed to HCPs; messages in outer packaging of the products). These measures are discussed below. The report also included the results of a survey conducted among PGEU members on the pharmacy dispensation settings reflecting that pharmacists provide patients with sufficient information on the safe use of these medicines when counselling in community pharmacies.

## **2.5. Discussion on additional risk minimisation measures**

Several risk minimisation measures were proposed during the procedure, particularly in light of the new safety evidence for the risks of PRES and RCVS. Some MAHs proposed to introduce educational materials for patients and HCPs, a patient card, as well as awareness campaigns for HCPs, in addition to the amendments of the product information and the dissemination of a direct healthcare professional communication (DHPC). These measures were also proposed by experts consulted during the procedure and part of the measures suggested by PGEU to be considered by PRAC (see section 2.4. ). It should be noted that the input of experts and PGEU on potential new risk minimisation measures was considered to be related to the overall safety profile of pseudoephedrine-medicinal products, and not only specifically related to the new risks of PRES and RCVS which were the focus of this assessment.

Regarding educational materials, the PRAC discussed also the possibility of recommending an electronic pop-up checklist, to be implemented to the pharmacy dispensation systems, aiming at supporting pharmacists in counselling patients before dispensing pseudoephedrine-containing medicinal products. However, PRAC noted that the implementation of educational materials in the electronic systems of community pharmacies is not under the control of the MAHs.

Overall, the PRAC noted that the safety profile of pseudoephedrine-containing products is well-known and that risks other than PRES and RCVS (e.g. cardiovascular and cerebrovascular events, particularly ischemic events and the risk of misuse and abuse) are addressed in the product information to varying extent, and are monitored via routine pharmacovigilance activities. Specifically for PRES and RCVS, risk minimisation measures such as educational materials, patient card and awareness campaigns were considered not proportionate considering the magnitude of the risks as reviewed.

## **3. Benefit-risk balance**

The PRAC considered that the data reviewed in the context of this referral procedure do not question the efficacy of pseudoephedrine-containing products as no new data were made available to change the already established benefit of these medicinal products in the respective approved indications. The place in therapy of pseudoephedrine-containing medicinal products as symptomatic treatment of cold/flu and allergic rhinitis was also confirmed by the experts consulted in the procedure. With respect to safety, the PRAC reviewed the totality of the data submitted during this review in relation to the risks of PRES and RCVS in the context of the overall safety profile of pseudoephedrine-containing medicinal products. The causal relationship between pseudoephedrine and PRES and RCVS was assessed and considered at least reasonably possible. This causality assessment was supported by a total of 34 serious cases of PRES and RCVS assessed as probably or possibly related to



pseudoephedrine, the literature articles describing pseudoephedrine as a trigger for PRES and RCVS, together with the plausible mechanism of pseudoephedrine action in PRES and RCVS development.

PRES is a neurological disorder caused by the dysregulation of cerebral perfusion. RCVS is a medical condition in which there is multifocal arterial constriction and dilation in the cerebral vasculature. Pseudoephedrine is described in the literature as a precipitant factor to the development of PRES and RCVS along with other vasoactive agents. Additionally, clinical data indicate that pseudoephedrine can cause a dose-dependent increase in blood pressure, which is a standard risk factor for cardiovascular and cerebrovascular complications including PRES and RCVS.

The number of case reports of PRES or RCVS identified as related to pseudoephedrine (n=34) was not considered high when comparing with the high patient exposure to pseudoephedrine. This was agreed by the experts consulted during the procedure. However, the PRAC noted that all the reported cases with pseudoephedrine were serious, led to hospitalisation and in 5 of the cases, recovery with sequelae was reported. Besides, the PRAC noted that PRES and RCVS are serious conditions, while usually reversible or resolved with prompt diagnosis and management. Despite not observed in the cases reviewed in association with pseudoephedrine use, cases of irreversible or fatal PRES have been reported, nonetheless. Additionally, life-threatening forms of RCVS with several strokes and uncontrolled massive brain oedema have been reported (not in association with pseudoephedrine). Early recognition and interventions are therefore key for achieving a favourable clinical outcome of PRES and RCVS. As a result, considering the seriousness of these syndromes, it is important to minimise their occurrence in patients treated with pseudoephedrine-containing medicinal products given the reasonable possible association between pseudoephedrine use and the development of PRES and RCVS as described above. Consequently, the product information of pseudoephedrine-containing medicinal products should be updated to inform HCPs and patients about PRES and RCVS, their signs and symptoms, and what actions should be taken in case the reactions occur (SmPC section 4.4 and corresponding package leaflet section(s)). Additionally, the adverse reactions should be added with an estimated frequency 'not known' to the product information (SmPC section 4.8 and corresponding package leaflet section).

Particularly on risk factors for PRES and RCVS, the PRAC noted the established link between severe hypertension and the risk of PRES and RCVS as well as the known hypertensive effects of pseudoephedrine. Patients with severe hypertension or uncontrolled hypertension treated with pseudoephedrine containing medicinal products are considered to be at an increased risk to develop PRES and RCVS. Separately, in multiple articles, impaired kidney function (renal disease, acute kidney injury, renal failure, end-stage renal disease and renal impairment) is reported as a significant risk factor for PRES and RCVS. Pseudoephedrine is primarily excreted by the kidneys. Renal impairment is known to increase plasma levels of pseudoephedrine and should not be used by those with severe renal impairment. Hence, patients with kidney disease/renal failure are at an increased risk of PRES and RCVS when taking pseudoephedrine-medicinal products. As a conclusion, the PRAC considered that patients with severe or uncontrolled hypertension and patients with severe acute or chronic kidney disease/renal failure should not be treated with pseudoephedrine-medicinal products and a contraindication should be added accordingly (SmPC section 4.3 and corresponding package leaflet section(s)).

A direct healthcare professional communication was also agreed, together with a communication plan, to inform relevant HCPs of the risks of PRES and RCVS with pseudoephedrine-containing medicinal products and the agreed amendments to the product information.

Further risk minimisation measures were discussed by the PRAC during the assessment, including educational materials, a patient card and awareness campaigns to HCPs. These measures were also discussed by the clinical experts consulted during the procedure and a part of the measures proposed



by one stakeholder. After careful consideration of the available evidence related to the risks of PRES and RCVS, these additional measures were not considered proportionate considering the magnitude of the risks. There was no new identified evidence related to other known risks associated with pseudoephedrine-containing medicinal products that could lead to a PRAC recommendation for further risk minimisation measure beyond the ones described above. In view of the above, the Committee considered that the benefit-risk balance of pseudoephedrine-containing medicinal products in its authorised indications remains favourable subject to the recommended amendments to the product information.

## **4. Summary of new activities and measures**

The Committee, having considered all information and data submitted in the procedure, recommended risk minimisation measures to further characterise and minimise the risks of PRES and RCVS.

### **4.1. Risk management**

#### **4.1.1. Safety concerns**

The Committee considered that the following safety concerns should be added as important identified risks: "posterior reversible encephalopathy syndrome (PRES)" and "reversible cerebral vasoconstriction syndrome (RCVS)" to the list of safety concerns for the PSURs.

#### **4.1.2. Risk minimisation measures**

##### **4.1.2.1. Routine risk minimisation measures**

##### **Amendments to the product information**

The PRAC considered that routine risk minimisation measures in the form of updates to the product information are necessary in order to minimise the risks of PRES and RCVS associated with the use of pseudoephedrine-containing medicinal products. These changes include amendments to sections 4.3, 4.4 and 4.8 of the SmPC.

Section 4.3 of the SmPC should be updated to include contraindications in patients with severe hypertension or uncontrolled hypertension and in patients with severe acute or chronic kidney disease/renal failure.

Section 4.4 should be updated to include warnings and precautions of use relating to the risks of PRES and RCVS, reflecting the current knowledge on the occurrence of these reactions and the measures to follow in case of symptoms or signs of PRES or RCVS.

Section 4.8 of the SmPC should be updated to reflect the adverse reactions 'posterior reversible encephalopathy syndrome (PRES)' and 'reversible cerebral vasoconstriction syndrome (RCVS)' with a frequency 'not known' respectively.

The package leaflet should be amended accordingly.

### **4.2. Direct Healthcare Professional Communication and Communication plan**

The Committee adopted the wording of a DHPC, to inform HCPs of the risks of PRES and RCVS with pseudoephedrine-containing medicinal products and associated risk minimisation measures including

the amendments to the product information. The Committee also agreed on a communication plan. This communication should be distributed to general practitioners, allergologists, otorhinolaryngologists, pharmacists, neurologists, emergency physicians, pneumologists and any other relevant target groups to be further defined at national level.

All concerned MAHs are encouraged to liaise with national competent authorities to collaborate in order to prepare and circulate a single DHPC in each Member State.

## 5. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data on pseudoephedrine-containing medicinal products.
- The PRAC reviewed the totality of the data available for pseudoephedrine-containing medicinal products in relation to the risks of PRES and RCVS in the context of the overall safety profile of the medicines. This included data available in EudraVigilance, in the literature, as well as the responses to the questions from PRAC submitted by the MAHs. The PRAC also considered the outcome of the consultation with an ad-hoc expert group and a submission by one stakeholder.
- The PRAC concluded that the efficacy of pseudoephedrine containing medicinal products in its approved indications is established.
- The PRAC concluded that the serious reactions of PRES and RCVS are important identified risks associated with the use of pseudoephedrine-containing medicinal products.
- The PRAC was of the view that the data reviewed raise concerns about the use of pseudoephedrine containing medicinal products in patients with severe or uncontrolled hypertension and in patients with severe acute or chronic kidney disease/renal failure, and concluded that the use of pseudoephedrine-containing medicinal products should be contraindicated in these patient populations.
- In addition, the PRAC concluded that there is a need to update the product information of these products to reflect the current knowledge on the occurrence of these reactions and the measures to follow in case of symptoms or signs of PRES or RCVS.

In view of the above, the Committee considers that the benefit-risk balance of pseudoephedrine-containing medicinal products remains favourable subject to the agreed amendments to the product information and other risk minimisation measures.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for pseudoephedrine-containing medicinal products.

## **Appendix 1**

### **Divergent position to PRAC recommendation**

## **Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data**

Procedure No: EMEA/H/A-31/1526

Procedure No: Aerinaze EMEA/H/A-31/1526/ C/000772/0047

Pseudoephedrine-containing medicinal products

### **Divergent statement**

The following PRAC Member considers that the benefit-risk balance of pseudoephedrine-containing products is not favourable based on the following grounds:

Pseudoephedrine, as single active substance or in fixed dose combinations, is used as short-term symptomatic relief of nasal or sinus congestion caused by the common cold, sinusitis, allergic rhinosinusitis or aerotitis. These medicines are only available in oral forms and are authorised for more than 35 years in Europe.

In February 2023, France triggered a referral procedure under Article 31 of Directive 2001/83/CE in view of new serious risks pointed out with the use of pseudoephedrine, i.e. Posterior Reversible Encephalopathy Syndrome (PRES) and Reversible Cerebral Vasoconstriction Syndrome (RCVS). The PRAC was especially asked to assess the overall benefit-risk balance of pseudoephedrine-containing medicinal products taking into consideration the overall safety profile of pseudoephedrine, including the risks of PRES/RCVS and all other known risks.

The PRAC concluded that a causal relationship between pseudoephedrine and the risks of PRES/RCVS is established. Some risk factors of PRES and RCVS have been identified and the PRAC recommended an update of the product information with additional contraindications (i.e. severe or uncontrolled hypertension, acute or chronic kidney disease) and a warning to further describe these adverse drug reactions and their clinical management in order to mitigate these risks. However, these risk minimisation measures are deemed insufficient since cases of PRES/RCVS have been reported without any risk factors or notable medical history and numerous contraindications are already in place nationally for some pseudoephedrine containing products. The compliance towards all these measures cannot be guaranteed in clinical practice in view of the approved therapeutic indications and the context of use of these medicines.

These newly identified risks of PRES and RCVS add to the already numerous serious ischaemic risks associated to pseudoephedrine use (cardiovascular events such as haemorrhagic or ischaemic strokes, myocardial infarction, ischaemic cardiomyopathies, ischemic colitis, etc.) which are still reported in France despite risk minimisation measures in place (such as contraindications and warnings in the product information).

The current indications of pseudoephedrine containing products in symptomatic relief of nasal or sinus congestion are benign, non-life threatening and self-resolving conditions. Pseudoephedrine is thus only a symptomatic treatment. In France, the ANSM with the support from several learned societies including ENTs (otolaryngologists), general practitioners, and pharmacists encourages the use of simple hygienic measures that are considered sufficient in the relief of common cold symptoms, and advises not to use vasoconstrictors as nasal decongestant considering the risk of serious adverse drug reactions. The identified vascular and ischaemic events associated to pseudoephedrine use can lead to death or life-threatening conditions with sequels in some cases. This accumulation of identified vascular and ischaemic risks considerably weighs down the safety profile of pseudoephedrine. Moreover, the proposed risk minimisation measures (product information updates with contraindications and warnings) are not expected to prevent any of these risks.

The time is coming to stop to collect the already considerable list of very serious adverse drugs reactions without reconsidering the very limited benefits of this symptomatic medicine.

Therefore, the benefit-risk balance of pseudoephedrine containing products is considered as negative.

**PRAC Member expressing a divergent opinion:**

- Tiphaine Vaillant (France)