NOTIFICATION TO THE PRAC /EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by France:

Product Name(s) in the Referring Member State, if applicable	Actifed rhume jour et nuit ; Actifed rhume ; Actifed LP Rhinite allergique ; Dolirhume paracetamol et pseudoephedrine 500 mg/30 mg ; Dolirhumepro paracetamol, pseudoephedrine et doxylamine ; Humex rhume ; Nurofen rhume ; Rhinadvil rhume ibuprofene/pseudoephedrine ; Rhinadvilcaps rhume ibuprofene/pseudoephedrine 200 mg/30 mg ; Aerinaze ; Rhumagrip
Active substance(s) *Please clarify name(s)*	Pseudoephedrine containing products (all indications)
Pharmaceutical form(s) *If all pharmaceutical forms are included, state "All".* *If not all pharmaceutical forms are included, please specify the one included.*	All
Strength(s) *If all strengths are included, state "All".* *If not all strengths are included, please specify the one included.*	All
Route(s) of Administration *If all routes of administration are included, state "All".* *If not all routes of administration are included, please specify the ones included.*	All
Marketing Authorisation Holders in the referring Member State	Reckitt Benckiser GSK santé grand public Johnson&Johnson Opella Healthcare France Urgo Healthcare France Coopération Pharmaceutique Française Organon

Background

Authorisations and indications

Pseudoephedrine is only available in the EU in oral forms, alone or in combination to antalgic, antipyretics, anti-histaminic or morphinic derivates.

Pseudoephedrine [PdE] (as single active substance or in fixed dose combinations) has been authorized for more than 35 years in Europe. The current indications of PdE-containing medicines include:

- Symptomatic relief of nasal/sinus congestion with headache, fever and pain associated with the common cold and flu in adults and adolescents over 12 or 15 years of age. This indication can slightly vary according to the country and Marketing Authorization Holder [MAH]. Most of medicinal products for "cold" indication are Nationally Authorised Products (NAPs).
- Treatment of the symptoms of seasonal allergic rhinitis (hay fever, inflammation of the nasal passages caused by an allergy to pollen) in patients who have nasal congestion (a blocked nose). For this indication there are NAPs and one Centrally Authorised Product (CAP), Aerinaze (pseudoephedrine/desloratadine).

Pharmacology

Vasoconstrictors, which include PdE, have direct sympathomimetic action by activation of alpha- and beta-adrenergic receptors. They also have indirect sympathomimetic action by increasing the release of noradrenaline in synaptic space.

Stimulation of alpha-1 adrenergic receptors located on the smooth wall of blood vessels in the nasal mucosa (post-capillary venules) results in vasoconstriction, decreased blood volume, and decreased nasal mucosal volume (nasal decongestion). Pseudoephedrine has also general action on alpha-adrenergic receptors leading to systemic effects (blood vessels constriction).

Known safety profile

The known safety profile of PdE includes serious adverse drug reactions such as strokes (haemorrhagic or ischaemic), myocardial infarction [MI] or ischaemic cardiomyopathies, hypertensive crisis or elevation in blood pressure. As part of previous Periodic Safety Update Report single assessment (PSUSA) procedures for ibuprofen/PdE, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended the update of the product information with the risk of ischaemic colitis and ischaemic optic neuropathy[1]. Apart from these serious ischaemic adverse drug reactions (ADRs), other recently reported risks with PdE use include Acute Generalized Exanthematous Pustulosis [AGEP]. All these risks are addressed in the product information of ibuprofen/PdE across the EU/EEA.
As PdE is similar to amphetamine, misuse and drug abuse have been reported in several countries, leading in some countries to marketing discontinuation.

Pharmacovigilance measures and characterisation of risks

Since the authorisation of PdE in Europe, actions have been taken in order to **better characterize the ischaemic risks**. The French National Agency for Medicines and Health Products Safety (ANSM) requested a pharmaco-epidemiological study to determine whether exposure to vasoconstrictors was associated with an increased risk of strokes and/or MI. The results of this case cross-over study became publicly available in 2021 and showed that the use of vasoconstrictor drugs was not associated with an increased risk of MI and strokes in individuals without a history of cardiovascular pathologies[2]. Although the study provided reassuring results about an absence of higher risk in patients without pre-existing cardiovascular risk factors, it concerned only non-lethal and non-disabling events (as patients had to answer themselves to questionnaires). As for all studies, there were limitations related to the design of this study and no conclusion was drawn about the risk of strokes and MI in patients with pre-existing risk factors and about the seriousness of risks (death, disability).

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1 PSUSA/00001711/201807 and PSUSA/00001711/201907

2 Grimaldi-Bensouda L, Begaud B, Benichou J, Nordon C, Dialla O, Morisot N, Hamon Y, Cottin Y, Serrano E, Abenhaim L, Touzé E. Decongestant use and the risk of myocardial infarction and stroke: a case-crossover study. Sci Rep. 2021 Feb 18;11(1):4160. doi: 10.1038/s41598-021-83718-8. PMID: 33603081; PMCID: PMC7893034.

Current risk minimisation measures in Europe

Routine risk minimisation measures (RMMs) include contraindications or precautions of use (e.g., around 15 contraindications for ibuprofen/PdE combinations, 30 in France for some products) especially in patients with pre-existing cardiovascular conditions. Other RMMs include changes in prescription status (prescription only medicines [POM]) or restrictions in the number of boxes delivered by pharmacists. In France, forms and information sheets have been disseminated annually since 2020 to address the main risks and remind the main contraindications before dispensation.

Issues to be considered

New safety data

France is Lead Member State for the assessment of PSUSAs for ibuprofen-PdE combination indicated in the symptomatic relief of nasal/sinus congestion due to common cold and flu. As part of the assessment for the latest concerned period (July 2021-July 2022; PSUSA/00001711/202207), a new serious risk was pointed out, i.e. **Posterior Reversible Encephalopathy Syndrome [PRES] and Reversible Cerebral Vasoconstriction Syndrome [RCVS]**. As part of this PSUSA, cumulative review were requested about the risk of RCVS and PRES. After a thorough assessment of submitted data, PRES/RCVS are considered as related to PdE use in view of the reported cases (spontaneous and literature case reports) including a compatible and suggestive time to onset with PdE use, the biological plausibility and the lack of alternative aetiologies for some patients **without any risk factors of PRES/RCVS**. PRES and RCVS are serious risks imputable to the vasoactive properties of PdE. They are associated with major and life-threatening complications like strokes. PdE is described in the literature as a cause of RCVS. Distinction between PRES and RCVS is still debated in the literature but it is mentioned that PRES could be a consequence of RCVS.

Need for benefit/risk reassessment

Measures have been discussed as part of the latest PSUSA ibuprofen-PdE (PSUSA-00001711-202207), in order to mitigate the risk of PRES/RCVS (e.g. update of the SmPC in the sections 4.3, 4.4, 4.8, package leaflet accordingly; educational material for patients and/or pharmacists, DHPC). According to France (LMS), these RMMs do not seem to be sufficient to prevent from all ischaemic events associated with PdE use.

At national level, in some EU countries, PRES/RCVS is already labelled for some pseudoephedrine-containing products. The set of data submitted as part of the latest PSUSA procedure enables to have a complete and up-to-date overview of the PRES/RCVS risk associated to PdE use. Given the seriousness of this new confirmed risk, the overall risk profile, particularly the ischaemic events, and the fact that RMMs appear not sufficient to mitigate all risks, a global discussion at PRAC level is deemed necessary.

Considering the mechanism of action, and the systemic effects of PdE, the risk of PRES/RCVS is not expected to vary according to the combination or the indication, and the reassessment of the benefit/risk ratio should include all PdE-containing products in all indications and all forms. It is noteworthy that current indications of PdE/ibuprofen (symptomatic relief of nasal/sinus congestion) are benign, non-life threatening and self-resolving conditions.

In summary, the accumulation of severe risks of ischaemic nature and the whole safety profile of PdE-containing products question the benefit-risk balance, in particular in view of the approved indications for these products.

In view of the above and the necessity to take an action at EU level, France considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its

recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CHMP on the basis of a recommendation of the PRAC.

Signed Date

CHRISTELLE RATIGNIER CARBONNEIL ID

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Date : 2023.02.03 17:00:47 +01'00'