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# France Advises Against Pseudoephedrine Use With EMA Safety Review Ongoing

by Tom Gallen

As EMA's ongoing safety review of OTC decongestant pseudoephedrine enters its tenth month, France has decided to take action before any recommendations are issued. National medicines regulator ANSM is advising consumers not to use pseudoephedrine to treat their cold symptoms, much to the dismay of the local consumer health industry.

France's medicines regulator ANSM is advising those suffering from colds this winter to avoid taking pseudoephedrine to treat their symptoms due to the risk of serious adverse effects.

ANSM issued its recommendation with a European-wide safety review of pseudoephedrine-containing medicines ongoing and not due to conclude until December at the earliest. The European Medicines Agency's Pharmacovigilance Risk Assessment Committee initiated the review in February at the request of ANSM after it flagged concerns about the risk to pseudoephedrine users of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS). (Also see "*Pseudoephedrine Safety Review Initiated In EU Over Link To Neurological Problems*" - HBW Insight, 13 Feb, 2023.)

In a statement directed at consumers, ANSM said pseudoephedrine medicines put users in danger of myocardial infarctions and strokes. While acknowledging the risk was "very low," the agency pointed out that these adverse reactions could occur regardless of dose and duration of treatment.

As EMA noted at the start of the safety review, pseudoephedrine-containing medicines have a known risk of cardiovascular and cerebrovascular ischemic events, including stroke and heart attacks, with restrictions and warnings already included in product information.

Indeed, ANSM has introduced even tighter restrictions in France, where since 2020 pseudoephedrine can only be sold following a consultation with a pharmacists. (Also see "*Tighter*

*Controls For Pseudoephedrine OTCs In France* " - HBW Insight, 3 Feb, 2020.)

But according to ANSM, these restrictions do not go far enough. The regulator has claimed that serious adverse events related to pseudoephedrine use continue to be reported.

While the message to French consumers not to take pseudoephedrine is currently only advisory, ANSM warns in its statement that more restrictive measures could be taken in future.

ANSM's advice will likely impact sales of eight non-prescription pseudoephedrine-containing products marketed in France:

- Actifed Rhume
- Actifed Rhume jour et nuit
- Dolirhume Paracétamol et Pseudoéphédrine
- Dolirhumepro Paracétamol Pseudoéphédrine et Doxylamine
- Humex Rhume
- Nurofen Rhume
- Rhinadvil Rhume Ibuprofène/Pseudoéphédrine
- Rhinadvilcaps Rhume Ibuprofène/Pseudoéphédrine

All eight are in tablet form and combine pseudoephedrine with an analgesic (paracetamol or ibuprofen 200 mg) and/or an antihistamine (doxylamine, chlorphenamine, triprolidine, diphenhydramine). Pseudoephedrine-containing nasal sprays are available in France only on prescription.

## Industry Not Happy

The statement issued by ANSM has unsurprisingly irked France's OTC manufacturers, with industry association NèreS describing the regulator's pseudoephedrine advice as premature and alarmist

With the EMA safety review – which NèreS is actively participating in – yet to conclude, the association said it was too early for ANSM to draw its own conclusions. The agency's

intervention was "surprising," NèreS said, given that it was ANSM which called for the EMA's involvement.

As ANSM has not withdrawn marketing authorizations, and given the fact the benefit/risk balance remains favorable, French consumers should continue to responsibly use pseudoephedrine-containing medicines, NèreS insisted.

Dispensing of pseudoephedrine followed a very strict protocol, the association said, through which the pharmacist ensures against contraindications and issues the patient with an information sheet prepared by the marketing authorization holder.

Following the start of the EMA review, NèreS said it had proposed updating these sheets to include information about the risks of PRES and RCVS, but this suggestion had been turned down by ANSM. Furthermore, the association and its members have proposed additional risk reduction measures for pseudoephedrine but have received no response from the regulator.

Despite this, NèreS said it remained eager to continue its discussions with ANSM.

NèreS pointed out that thanks to work carried out in France to ensure pseudoephedrine is taken correctly, use of the medicine was among the lowest in Europe. While 14,721 boxes per 100,000 inhabitants was the European Union average in 2022, France dispensed just under 6,000 boxes per 100,000.

## EMA Review Continues

EMA's PRAC continues to regularly discuss the safety of pseudoephedrine. At its meeting held from 25-28 September meeting, the committee received feedback from its ad-hoc expert group meeting and adopted its second list of outstanding issues.

Rapporteur/co-rapporteur joint assessment reports are due to be circulated to PRAC and to EMA's Committee for Medicinal Products for Human Use throughout November. In December, PRAC is timetabled to either issue its recommendation to CHMP or if this is not possible, draw up an updated list of outstanding issues.

Marketing authorization holders for pseudoephedrine-containing drugs have played an active role in the process. They were initially sent a list of questions by PRAC to help it establish the risk of PRES and RCVS when using these products. As part of their response, MAHs were asked to provide proposals and justifications for current and further risk minimization measures which could prevent or mitigate the risks of cerebrovascular events, including PRES and RCVS.

While Europe assesses the benefit/risk balance of pseudoephedrine, across the Atlantic it is another OTC vasoconstrictor, phenylephrine, which is under the spotlight. (Also see

"*Phenylephrine: EU Manufacturers, Don't Panic, But May Be Time To Prepare*" - HBW Insight, 19 Oct, 2023.)

In September, a US Food and Drug Administration advisory committee unanimously voted that results of research presented by the agency show oral phenylephrine at OTC monograph doses is ineffective to treat nasal congestion. FDA said afterward that it "will consider the input of this advisory committee, and the evidence, before taking any action on the status of oral phenylephrine" as part of the OTC cough, cold, allergy, bronchodilator and antiasthma monograph. (Also see "*Fast Start To Oral Phenylephrine Efficacy Complaints As US FDA Considers 'Any Action'*" - HBW Insight, 14 Sep, 2023.)