EMA confirms measures to minimise the risk of serious side effects with medicines containing pseudoephedrine

29/01/2024 | Circular Number P02/2024

Information on pseudoephedrine

- Pseudoephedrine works by stimulating nerve endings to release the chemical noradrenaline, which causes the blood vessels to constrict (narrow). This reduces the amount of fluid released from the vessels, resulting in less swelling and less mucus production in the nose.
- Pseudoephedrine-containing medicines are authorised in various EU Member States and are used alone or in combination with other medicines to treat symptoms of cold and flu, such as headache, fever and pain, allergic rhinitis (inflammation of the nasal passages from allergies) or vasomotor rhinitis (inflammation of the nasal passages from non-allergic or non-infectious causes), in people with nasal congestion. Pseudoephedrine is also authorised in some EU Member States to treat aerotitis (inflammation of the middle ear due to sudden changes in air pressure) in a fixed-dose combination with triprolidine.
- Within the EU, pseudoephedrine-containing medicines are available under various trade names including Actifed, Clarinase, and Nurofen Cold and Flu.

The following products are authorised via various procedures.

Active Ingredients	Product Name	Pharmaceutical Form	Classif-cation	Authorisation Number	MAH/license holder
Pseudoephedrine hydrochloride 30 mg(s)/5 ml | triprolidine hydrochloride 1.25 mg(s)/5 ml	Actified	Syrup	Authorised	PI274/01301A	Alfred Gera & Sons Limited
Loratidine 5 mg(s) | Pseudoephedrine sulfate 120 ml(s)	Clarinase Repetabs	Prolonged-release tablet	Authorised	MA897/00201	Bayer SA-NV
Paracetamol 500 mg(s) | pseudoephedrine hydrochloride 30 mg(s) | dextromethorphan hydrobromide 15 mg(s) | ascorbic acid 60 mg(s)	Parcoten Cold & Flu	Film-coated tablet	Authorised	AA115/01703	Delorbis Pharmaceuticals Limited
Triprolidine hydrochloride 1.25 mg(s)/5 ml | guaifenesin 100 mg(s)/5 ml | pseudoephedrine hydrochloride 30 mg(s)/5 ml	Actifed Expectorant Oral Solution	Oral solution	Authorised	MA192/02003	Glaxo SmithKline Ireland Limited

Guaifenesin 100 mg(s)/5 ml | triprolidine hydrochloride 1.25 mg(s)/5 ml | pseudoephedrine hydrochloride 30 mg(s)/5 ml	Actifed Expectorant	Oral solution	Authorised	MA192/02004	Glaxo SmithKline Ireland Limited
Ibuprofen 200 mg(s) | pseudoephedrine hydrochloride 30 mg(s)	Advil Cold & Flu	Coated tablet	Authorised	MA460/01001	GlaxoSmithKline Consumer Healthcare (Ireland) Limited
Pseudoephedrine hydrochloride 30 mg(s) | paracetamol 500 ml(s)	Panadol Cold & Flu	Film-coated tablet	Authorised	MA1177/00701	Haleon Hellas
Diphenhydramine hydrochloride 12.5 mg(s) | paracetamol 500 mg (s) | pseudoephedrine hydrochloride 22.5 mg(s)	Benylin Four Flu	Film-coated tablet	Authorised	MA1315/00204	Johnson & Johnson (Ireland) Limited
Triprolidine hydrochloride 1.25 mg(s)/5 ml | pseudoephedrine hydrochloride 30 mg/5 ml	Actifed	Syrup	Authorised	AA770/17501	JV Healthcare Limited
Pseudoephedrine hydrochloride 30 mg(s)/5 ml | triprolidine hydrochloride 1.25 mgs)/5 ml	Actifed	Syrup	Authorised	AA521/09201	Medicem Limited
Pseudoephedrine hydrochloride 15 mg(s) | chlorphenamine maleate 1 mg(s) | paracetamol 325 mg(s)	Snip	Tablet	Authorised	MA032/06401	Medochemie Limited
Paracetamol 325 mg(s) | pseudoephedrine hydrochloride 15 mg(s) | chlorphenamine maleate 1 mg(s)	Snip	Tablet	Authorised	MA032/06402	Medochemie Limited
Triprolidine hydrochloride 1.25 mg(s) | pseudoephedrine hydrochloride 30 mg(s)	Medofed	Oral Solution	Authorised	MA032/03101	Medochemie Limited
Pseudoephedrine hydrochloride 30 mg(s) | triprolidine hydrochloride 1.25 mg(s)	Medofed	Oral Solution	Authorised	MA032/03104	Medochemie Limited
Triprolidine hydrochloride 1.25 mg(s)/5 ml | guaifenesin 100 mg(s)/5 ml | dextromethorphan hydrobromide 15 mg(s)/5 ml | pseudoephedrine hydrochloride 20 mg(s)/5 ml	Medofed Compound	Oral Solution	Authorised	AA032/03105	Medochemie Limited
Loratadine 5 mg(s) | pseudoephedrine sulfate 120 mg(s)	Clarityne-D	Prolonged-release tablet	Authorised	PI908/00601A	NeoFarma Pharmaceuticals Limited

Triprolidine hydrochloride 1.25 mg(s)/5 ml | pseudoephedrine hydrochloride 30 mg(s)/5 ml	Actifed	Syrup	Authorised	AA908/26001	NeoFarma Pharmaceuticals Limited
Cetirizine dihydrochloride 5 mg(s) | pseudoephedrine hydrochloride 120 mg(s)	Cirrus	Prolonged-release tablet	Authorised	PI908/17202A	NeoFarma Pharmaceuticals Limited
Pseudoephedrine hydrochloride 60 mg(s)	Sudafed Decongestant	Film coated tablet	Authorised	AA908/09901	NeoFarma Pharmaceuticals Limited
Paracetamol 500 mg(s) | pseudoephedrine hydrochloride 30 mg(s)	Panadol Cold and Flu	Film coated tablet	Authorised	PI908/10501A	NeoFarma Pharmaceuticals Limited
Pseudoephedrine hydrochloride 30 mg(s) | paracetamol 500 mg(s)	Prosinus	Film coated tablet	Authorised	AA1438/11801	NM Pharma Limited
Ibuprofen 200 mg(s) | pseudoephedrine hydrochloride 30 mg(s)	Nurofen Cold & Flu	Film coated tablet	Authorised	MA1447/00104	Reckitt Benckiser Ireland Ltd
Ibuprofen 200 mg(s) | pseudoephedrine hydrochloride 30 mg(s)	Brupro Cold & Flu	Film coated tablet	Authorised	AA041/00901	Rowa Pharmaceuticals Limited
Paracetamol 325 mg(s) | pseudoephedrine hydrochloride 30 mg(s) | dextromethorphan hydrobromide 15 mg(s)	Daleron COLD3	Film coated tablet	Authorised	MA982/02701	TAD Pharma gmbh
Cetirizine dihydrochloride 5 mg(s) | pseudoephedrine hydrochloride 120 mg(s)	Cirrus	Prolonged Release Tablets	Authorised	MA030/00801	UCB Pharma SA
Pseudoephedrine hydrochloride 60 mg(s)	Non-Drowsy Sudafed Decongestant	Film-coated Tablets	Authorised	AA288/00802	V.J. Salomone Pharma Limited

Information from the EMA about the safety concern

- On 25 January 2024, EMA's human medicines committee (CHMP) endorsed the measures recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) to minimise the risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) for medicines containing pseudoephedrine.
- PRES and RCVS are rare conditions that can involve reduced blood supply to the brain, potentially causing serious, life-threatening complications. With prompt diagnosis and treatment, symptoms of PRES and RCVS usually resolve.
- CHMP confirmed that medicines containing pseudoephedrine are not to be used in patients with high blood pressure that is severe or uncontrolled (not being treated or

resistant to treatment) or in patients with severe acute (sudden) or chronic (long-term) kidney disease or failure.

- In addition, healthcare professionals should advise patients to stop using these medicines immediately and seek treatment if they develop symptoms of PRES or RCVS, such as severe headache with a sudden onset, feeling sick, vomiting, confusion, seizures and visual disturbances.
- The recommendations follow a review of all available evidence, including post-marketing safety data, which concluded that pseudoephedrine is associated with risks of PRES and RCVS. During the review, Pharmacovigilance Risk Assessment Committee (PRAC) which is the Committee responsible for the evaluation of safety issues for human medicines, sought advice from an expert group of general practitioners, otorhinolaryngologists (specialists in diseases of the ear, nose, throat, head and neck), allergologists (specialists in the treatment of allergies) and a patient representative. PRAC also considered information submitted by a third-party representing healthcare professionals.
- The review of pseudoephedrine-containing medicines was initiated at the request of the French medicine agency, under Article 31 of Directive 2001/83/EC.
- The review was first carried out by the PRAC, which made a set of recommendations. The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's opinion.
- The product information for all pseudoephedrine-containing medicines will be updated to include the risks concerning PRES and RCVS and the new measures to be taken. Restrictions and warnings are already included in the product information of these medicines to reduce cardiovascular and cerebrovascular ischaemic (involving reduced blood supply to the heart and brain) risks.
- The CHMP opinion will now be sent to the European Commission, which will issue a legally binding decision across the EU.

Information for patients

- An EU-wide review has found that pseudoephedrine-containing medicines can cause posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS), rare conditions that can involve reduced blood supply to the brain. This follows an evaluation of all available data including few reported cases of these conditions.
- Do not take pseudoephedrine-containing medicines if you have high blood pressure that is severe or uncontrolled (not being treated or resistant to treatment) or if you have severe acute (sudden) or chronic (long-term) kidney disease or failure, as these are risk factors for developing PRES or RCVS.
- Stop using pseudoephedrine-containing medicines immediately and seek urgent medical assistance if you develop symptoms of PRES or RCVS such as a severe headache with a sudden onset, feeling sick, vomiting, confusion, seizures and changes in vision.

- If you have any questions or concerns about your medicines, speak to your doctor or pharmacist.

Information for Healthcare Professionals

- An EMA review has found that pseudoephedrine-containing medicines are associated with risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS), serious conditions affecting the cerebral blood vessels. This follows an evaluation of all available data including few reported cases of these conditions.
- There were no fatal cases of PRES or RCVS reported, and most of the cases resolved following discontinuation of the medicine and appropriate treatment.
- Pseudoephedrine-containing medicines must not be used in patients with severe or uncontrolled hypertension or severe acute or chronic kidney disease or renal failure, as these are risk factors for developing PRES or RCVS.
- Patients should be advised to discontinue treatment and seek immediate medical assistance if they develop symptoms of PRES or RCVS such as sudden, severe headache or thunderclap headache, nausea, vomiting, confusion, seizures and/or visual disturbances.
- The risks of PRES and RCVS should be considered alongside other risks associated with pseudoephedrine-containing medicines, including cardiovascular or ischaemic events.

A direct healthcare professional communication (DHPC) will be sent in due course to healthcare professionals prescribing, dispensing or administering the medicine. The DHPC will also be published on a dedicated page on the MMA website.

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance with pseudoephedrine containing medicines. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form and sending it to: Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 **or** online to http://www.medicinesauthority.gov.mt/adrportal or to the marketing authorisation holder or their local representatives.

Post-Licensing Directorate

Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Feedback Form

The Malta Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health.

The Malta Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this form (address side up), stapling the ends and then posting (no stamp required).

Feedback:

We thank you for your interest and look forward to hearing your opinion.

Postage will be paid
by the Licensee

No postage stamp
necessary if posted
in Malta and Gozo

BUSINESS REPLY SERVICE

Licence no. 656

Pharmacovigilance Section

Post-Licensing Directorate

Medicines Authority

Sir Temi Żammit Buildings

Malta Life Sciences Park

San Ġwann SĠN 3000