Annex II

Scientific conclusions

Scientific conclusions

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.

The PRAC adopted a recommendation on 30 November 2023 which was then considered by the CHMP, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

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.

Grounds for PRAC 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.
- 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 PRAC concluded that the benefit-risk balance of pseudoephedrine-containing medicinal products is favourable subject to changes to the product information as described above.

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

The Committee also agreed on the content of a direct healthcare professional communication together with a communication plan for its distribution.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

The CHMP, as a consequence, considers that the benefit-risk balance of pseudoephedrine-containing medicinal products remains favourable subject to the amendments to the product information described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for pseudoephedrine-containing medicinal products.