EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report for suppositories containing terpenic derivatives

INN/active substances: camphor, cineole, niaouli, wild thyme, terpineol, terpine, citral, menthol and essential oils of pine needle, eucalyptus and turpentine

Procedure number: EMEA/H/A-1284

Referral under Article 31(2) of Directive 2001/83/EC, as amended

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 27 October 2010, France triggered a referral under Article 31(2) of Directive 2001/83/EC, as amended. The CHMP was requested to give its opinion on whether the marketing authorisations for suppositories containing terpenic derivatives, should be maintained, varied, suspended or revoked for use in children less than 30 months.

The procedure described in Article 32 of Directive 2001/83/EC, as amended, was applicable.

2. Scientific discussion

2.1. Introduction

Suppositories containing terpenic derivatives have been authorised through national procedures in Europe since the 1950s and are currently authorized and marketed in 7 European countries (France, Belgium, Portugal, Spain, Italy, Luxembourg and Finland). Patient exposure is the largest in France, followed by Spain and Italy but usage patterns do not vary widely between countries. The products are currently marketed with the following indications:

- Adjunctive (or supportive) treatment of benign acute bronchial disorders.
- Airway diseases associated with cough and expectoration
- Fluidizing and expectorant in acute and chronic respiratory tract disorders
- Symptomatic treatment of respiratory disorders accompanied by cough and phlegm
- Symptomatic treatment of non productive cough
- Antipyretic treatment during benign acute bronchial episodes
- Prophylaxis and treatment of inflammatory diseases of upper airways. Cough, flu situations, acute and chronic catarrh of respiratory airways (bronchitis)

French safety review of use of suppositories containing terpenic derivatives in children

In 1996, the French MA Advisory Group established two lists of terpenic derivatives, based on toxicology and pharmacovigilance data. Group A includes terpenic derivatives with well documented potential toxicity (camphor, eucalyptol or cineole, menthol, levomenthol; essential oil of eucalyptus, niaouli, cajeput, and mint) while Group B includes terpenic derivatives with less well documented potential toxicity (terpineol, terpinol, thymol, alpha-pinene, beta-pinene, eugenol, linalol, and carvacrol; essential oil of pine, fir, turpentine, anise, Chinese anise tree, serpolet, clove, and cedar). Terpenic derivatives belonging to group A were contraindicated in children less than 30 months when used by cutaneous or inhaled route. This contraindication was also applied to children with a history of febrile convulsions, for terpenic derivatives belonging to groups A and B.

A first safety review was performed in 2006 and 2007 by the Afssaps and focused on available safety data provided by the MAHs of suppositories containing terpenic derivatives (from 1997 to the end of 2005 or 2006 depending on the MAH).

A second safety review of use of suppositories containing terpenic derivatives in children was completed in May 2010, following the identification of a potential neurological risk, mainly represented by convulsions, based on more recent cases since June 2007 from the national pharmacovigilance database and cases received by MAHs since 1997.

A total of 92 cases of adverse drug reactions (ADRs) were identified in the national pharmacovigilance database and the Periodic Safety Update Reports (PSURs), with about 82% (76/92) of these cases occurring in children less than 30 months. Thirty cases related to neurological disorders, including convulsions without hyperthermia (11 cases), agitation (5 cases), convulsive equivalent, hyperthermic convulsions, status epilepticus with intensive care management, hallucinations, hypothermia and somnolence. Twenty-one serious cases with plausible relationship were reported and for the cases where time to onset was reported, the neurological ADRs occurred on the day of treatment initiation. The outcome was favourable in all cases. There were also 47 cases of drug misuse, of which 42 were not associated with any ADRs. Medication errors included 5 neurological ADRs. In most cases, the

errors concerned the use of a child formulation instead of the infant formulation. Six cases of local irritation and one case of rectorrhagia with favourable outcome were notified, together with 12 cases of cutaneous ADRs and 2 cases of respiratory ADRs.

Based on these results, the National Pharmacovigilance Board and the MA Advisory Group recommended a contraindication of suppositories containing terpenic derivatives in children less than 30 months (in line with other routes of administration of terpenic derivatives in France) and children with history of febrile convulsion or epilepsy.

France subsequently circulated a Non-Urgent Information (NUI) to all member states to gather information on authorised suppository products containing terpenic active ingredients for children less than 30 months, including camphor, cineole, niaouli, wild thyme, terpineol, terpine, citral, menthol and essential oils of pine needle, eucalyptus and turpentine. Based on the NUI responses, France considered that the concerns of a potential neurological risk, mainly represented by convulsions associated with the use in children of terpenic medicines warranted a Community-level assessment. France therefore submitted a notification to the CHMP on 27th October 2010, requesting a referral procedure under Article 31(2) of Directive 2001/83/EC, to assess the benefit-risk of suppositories containing terpenic derivatives in children less than 30 months. The procedure started in November 2010.

2.2. Assessment of clinical efficacy and safety

Camphor, cineole (eucalyptol) and menthol

Regarding suppositories containing camphor, eucalyptol and menthol, the MAH stated that there is a lack of medicinal/scientific data (no available data in the MAH pre-clinical and clinical files and no data published in the scientific literature) but that no post-marketing spontaneous report was received from any source during the period of marketing in France. Consequently, the MAH could not perform any analysis on the possible risk factors/predictability of nervous system adverse reactions for cineole.

The CHMP noted the absence of spontaneous data. The MAH mentioned a recent published study in Pediatrics by Paul et al., 2010, investigating the efficacy and safety of a single topical application of a camphor, menthol and eucalyptus oil ointment on chest and neck as compared to no treatment for nocturnal cough, congestion and sleep difficulty caused by upper respiratory tract infections (URTI) in children aged 2 to 11 years. While the study was not designed to demonstrate the efficacy of terpenic derivatives suppositories in treatment of cough in children, it confirmed the occurrence of AEs with terpenic derivatives. It is noteworthy that some irritant adverse events (AEs) were only reported among children treated with the ointment; especially burning sensation of skin/nose/eyes, but also skin rash, and skin redness. Nervous system disorders (hyperactivity, sleepiness, headache) were also reported.

The CHMP also noted that safety measures have previously been implemented in France with regard to camphor-containing medicinal products, due to neurological adverse events reported in children. In 1980-1982, a national pharmacovigilance inquiry led to the contraindication of camphor-containing products used in topical formulations or on respiratory mucous membrane in children less than 30 months. In 1990-1992, another inquiry was conducted regarding hyperthermic convulsions and drug risk factor, identifying terpenic medicinal products as medications with a risk to induce convulsions. In 1994, the contraindication in children less than 30 months was extended to all medicinal products containing camphor as active substance. Finally, in 1996, following a benefit/risk review of terpenes-containing products, the contraindication was extended to products containing camphor as excipient. A contraindication in children with a history of convulsions was also included in the SmPC.

The CHMP also noted other regulatory actions taken by the Afssaps regarding adverse effects related to cosmetic products containing terpenic derivatives used in the paediatric population. In 2004, the Afssaps requested the withdrawal from the market of a cosmetic product containing about 6% of eucalyptol, because of the occurrence of serious neurological adverse effects (seizures) related to its application in infants. In 2006, the Afssaps requested the withdrawal from the market of a lotion containing high concentrations of terpenic derivatives, as the product did not mention precautions regarding its use in infants and children, and had caused serious neurological adverse events. Finally, in 2007 and 2008, a further product containing eucalyptol was withdrawn following three serious neurological adverse events reported in infants.

Niaouli

Regarding suppositories containing niaouli essential oil or niaouli essence, the MAH stated that only limited toxicity data exists. However, a number of toxicity studies have been performed on the main terpenic component of niaouli essential oil, eucalyptol. While acknowledging that the existing studies do not represent a complete toxicological program as required according to the current regulations, the MAH argued that eucalyptol is a well-known product.

The CHMP noted 6 ADRs (all serious) reported in PSURs during the period from April 2001 to December 2010, including general disorders (anaphylactic shock), skin and subcutaneous disorders (giant urticaria, rash maculopapular and Stevens Johnson-syndrome) and nervous system disorders (disorientation, visual hallucination). In addition, there was one case of dispensing error, without any ADRs, in which a suppository for children instead of a suppository for infants was dispensed to a 18-month-old child weighing 11 kg.

Additional non-serious cases were reported to the French regulatory authority during the review period, including 1 case of local ADR (burning sensation with anal pruritus), 15 cases of administration error of a child formulation instead of the infant formulation. In most of these cases, there was more than one child in the household.

Regarding the assessment of the toxicity of eucalyptol, the main terpene contained in niaouli essence, the CHMP noted a number of preclinical studies on eucalyptol, together with data on acute toxicity of eucalyptol in clinical studies as well as in paediatric population, evidencing neurological ADRs (in particular convulsions) when used by cutaneous and inhaled route, although no studies were identified using the rectal route of administration. Neurological ADRs have also been reported in the context of age-related administration errors. The CHMP listed several literature articles confirming that eucalyptol can induce convulsions in humans (Corrigan D, 1992, Craig J, 1953, Gurr GW & Scroggie JG,1965, Jonville APE et al., 1991,Millet Y et al., 1981, Patel S & Wiggins J , 1980, Spoerke DG et al., 1989, Steinmetz MD et al. 1987, Stafstrom CE, 2007, Day LM et al. 1997, Tibballs J, 1995, Vincens M, 1982 and Webb NJA & Pitt WR, 1993).

Thymus vulgaris and cineole

Regarding suppositories containing Thymus vulgaris and cineole, the MAH stated that no substantial new safety trends or signals were observed in safety data from the current post-marketing period that would indicate any change to the benefit-risk profile of the product or that would warrant updating reference safety information in the product data sheet. All studies agree that these compounds are effective in remission of symptoms associated with respiratory infections, especially cough, with no report of serious adverse effects. It is not possible to differentiate by age, as no specific studies in children have been published.

The CHMP noted that the products contained liquid extract of Thymus vulgaris, which includes 7 terpenic derivatives (β-myrcene, γ-terpinene, ρ-cymene, linalol, terpinen-4-ol, thymol, carvacrol). The CHMP assessed the literature review performed by the MAH on the terpenic active ingredient of the product as well as on the terpenic excipient, cineole (eucalyptol). The review did not identify any efficacy and safety study on suppositories using thyme alone, instead the published studies involved oral treatments (syrup or spray form) with thyme combination. In these studies, the products were indicated for treatment of acute bronchitis with productive cough, upper respiratory tract infections (URTIs), productive cough complaints, symptoms of cough. All studies included adults, except one which included children and adolescents between 2 and 17 years of age. The lack of randomised, doubled-blind, controlled studies was also noted, as most studies were open label. In addition, safety data from PSURs covering the period from 1997 to 2010 reported 2 non-serious cases of dermatitis but no serious ADRs, nervous system disorders or other safety concern were identified in spontaneous reports or literature reviews of clinical studies regarding oral products containing thymus.

The CHMP considered that the non-clinical data provided by the MAH indicate that neurological disorders may occur following exposure to several components of suppositories containing terpenic derivatives: overexposure to eucalyptol, sulfogaïacol and sodium camphosulfonate led to effects on vital functions such as neurological effects (mild sedation) or cardiovascular effects (bradypnnea). Severe effects were only observed following oral administration of isolated substances e.g. carvacrol or thymol for which CNS depression, ataxia, coma and respiratory failure were observed. In the absence of data investigating the dose-relationship of ADRs (especially nervous system disorders), no formal quantitative risk assessment could be made but the severity of the effects is anticipated to be dose related. Adequate safety pharmacology studies allowing specific assessment of the vital functions are

lacking. Moreover, the provided data did not allow any assessment of the risk in children because of the absence of studies performed in juvenile animal where, as in humans, minimal toxic dose level are expected to be lower due to the immaturity of the hepatic metabolism and the blood brain barrier.

The CHMP concluded that based on the spontaneous reporting (taking into account expected underreporting for non-prescription products) and in the absence of comparative studies, pooled analyses and meta-analyses comparing toxicity of terpenic derivatives used by rectal route the safety concerns raised by terpenic derivatives in children less than 30 months cannot be ruled out for Thymus vulgaris.

Citral

Regarding suppositories containing citral, the MAH submitted mainly non clinical studies and focused on experimental properties of citral and other phenolic compounds, to justify efficacy. From January 1998 to August 2009, a total of 18 cases of ADRs involving suppositories containing citral were reported, of which 10 were serious. Nervous system disorders were reported in 11 cases (7 serious): 4 serious cases of convulsions; 3 non-serious cases of agitation (medication errors in 2 cases); 1 case of somnolence (related to medication error); 2 serious cases of hypersomnia; and 1 serious case of hypotony (with malaise). A total of 7 medication errors were reported, all due to errors in the age formulation delivered. No ADRs were reported in the 4 remaining medication error cases.

In 6 cases, the citral-containing suppositories were associated with the reported cases of nervous system disorders, including malaise with loss of consciousness, convulsions and breathing difficulties, somnolence, three cases of agitation including one with mydriasis on one eye and myosis on the other eye and hypotonia. Other etiologies or significant medical history are confounding factors in 5 cases of neurological disorders; however the role of suppositories with citral as triggering factor of convulsion cannot be excluded. The cases included convulsive state, generalized convulsive seizure, convulsions and hypersomnia.

In summary, despite the confounding factors in 5 cases of neurological disorders reported with suppositories for infants containing citral, the CHMP concluded that citral could be a triggering factor of convulsion.

Cineole (eucapyptol), pine essential oil and guaiacol

Regarding suppositories containing cineole (eucalyptol), pine essential oil and guaiacol, the MAH stated that the products have been marketed since the 1960s and used as supportive therapy in benign acute bronchial disorders. From 1998 to 2010, 13 cases were reported in infants, 9 of which were related to administration errors (confusion between infant and child formulations), without any clinical consequence. In the 4 other cases, 2 severe AEs (somnolence and bronchospasm) could be related to the product. The MAH acknowledged that the benefit is modest and based on traditional use but stated that the products could be useful to allow parents to care for infants suffering from acute benign bronchial obstruction. The CHMP noted the case reports and concluded that suppositories containing cineole and pine are very likely to be associated with the 4 cases reported during the review period.

Turpentine and pine essence

Regarding suppositories containing turpentine, the MAH stated that significant therapeutic efficacy in the authorized indication has been reported by doctors prescribing these products and that adverse events have never been reported. However, the CHMP was of the opinion that the available evidence supports the neurological risks of terpenic derivatives as a family of substances.

2.3. Risk management plan

The CHMP did not require the MAH to submit a risk management plan.

2.4. Overall benefit/risk assessment

Benefits

In member states where they are authorised, suppositories containing terpenic derivatives have been used for decades as treatment for benign acute bronchial disorders or oropharynx congestive states,

particularly for non productive cough. Camphor, menthol and eucalyptol are the most studied substances from a preclinical and clinical point of view. Efficacy is based mainly on traditional use of these products and supported by data regarding pharmacodynamic properties and by their effects as cough suppressants and anti-inflammatory drug in pre-clinical models. Most clinical data are derived from open studies as well as data from clinical practice or expert opinions. However, there is no clinical data derived from comparative studies (randomized, double-blind and controlled studies), pooled analyses or meta-analyses comparing efficacy of terpenic derivatives used by rectal route. No studies focused on children less than 30 months are available.

Risks

The main data was obtained from spontaneous reports, the literature and pre-clinical data. The CHMP reviewed a number of publications confirming that terpenic derivatives can induce convulsions in humans. A number of adverse drug reactions, including serious nervous system disorders were reported in paediatric patients, including convulsions, agitation, somnolence, hypersomnia, hypotonia, disorientation, and hallucination. When taking into account all system organ classes, the reported adverse drug reactions (ADRs) were mainly nervous system disorders. Other disorders including skin disorders and respiratory disorders were also identified. Rectal lesions, including rectal burning, are of particular concern because of their severity and because they represent a limiting factor for treatment duration. The CHMP also noted that underreporting due to the non-prescription status can be assumed. Finally, dispensing or administration errors were also identified with cases where the administered/prescribed suppository was not suitable for the age or weight of the child.

The CHMP also reviewed the French safety assessment of the use of suppositories containing terpenic derivatives in children, completed in May 2010. A total of 92 cases of ADRs were identified in the national pharmacovigilance database and the periodic safety update reports, with about 82% (76/92) of these cases occurring in children less than 30 months. Thirty cases related to neurological disorders, and twenty-one serious cases with plausible relationship were reported. For the cases where time to onset was reported, the neurological ADRs occurred on the day of treatment initiation. Medication errors included 5 neurological ADRs. In most cases, medication errors involved the use of a child formulation instead of the infant formulation. Six cases of local irritation and one case of rectorrhagia with favourable outcome were notified, together with 12 cases of cutaneous ADRs and 2 cases of respiratory ADRs.

The CHMP also noted that terpenic derivatives administered by other route of administration (cutaneous and inhaled) are associated with risks of neurological, skin, and local toxicity. While acknowledging that direct comparisons of suppositories containing terpenic derivatives regarding these aspects are lacking and that suppositories could be a therapeutic alternative in children who do not tolerate treatment with ointments, the CHMP was of the opinion that the available data confirms that the safety profile of terpenic derivatives used by rectal route in infants and children is of concern.

From a mechanistic point of view, based on the pharmacological properties of terpenic derivatives, these substances are non-polar (or lipophilic) compounds which show an affinity for non-polar human body structures. This is of particular concern in children and infants, who have little fatty mass, as these substances instead cross into the central nervous system (CNS), practically the only apolar structure at that age. Moreover, suppositories are known to distribute systemically, due to product absorption through the rectal mucous membrane which is particularly vascularised.

The CHMP also noted that the limited available data made it impossible to establish whether a direct relationship exists between the administered dose and the ADRs observed. The CHMP considered this to be of concern, especially when considering cases where children were exposed to an inadequate dosage or suppository formulation, for example due to parents using suppositories dispensed for older children in other younger children or infants in the family.

Risk minimisation measures

In its assessment, the CHMP requested the MAHs to propose risk minimisation measures to address the identified risks. Having assessed the proposals submitted by the MAHs (including the introduction of special warnings, a lower weight limit, limiting treatment duration, a contra-indication in case of history of convulsions or epilepsy and highlighting the risk of interaction with other products containing terpenic which could result in an increased risk of neurological side effects), the CHMP considered that in addition to the measures proposed, a contraindication in children less than 30 months was necessary to adequately manage the risk profile of suppositories containing terpenic derivatives. The CHMP also considered it necessary to restrict the duration of treatment in the remaining approved

paediatric population to 3 days, due to risk of rectal burning and to the risks related to storage of terpenic derivatives in tissues and brain (the rate of metabolism and elimination is unknown, as a consequence of their lipophilic properties) which can lead to neuropsychological disorders.

Benefit/Risk balance

Having considered the totality of the data submitted by the MAHs related to the use of suppositories containing terpenic derivatives in children less than 30 months and taking into account the data identified during the 2010 French safety review, the CHMP was of the opinion that suppositories containing terpenic derivatives can induce neurological disorders, especially convulsions, in children less than 30 months, due to the immaturity of the central nervous system which results in a higher susceptibility to neurological toxicity. In addition, the suppositories can also be associated with the risk of rectal burning. The risk minimisation measures proposed by the MAHs were considered insufficient to reduce the neurological risk to an acceptable level in children less than 30 months.

Limited clinically relevant efficacy has been demonstrated in the paediatric population. In children less than 30 months, no data on efficacy is available.

As a consequence, taking into account the risk of neurological toxicity and other adverse events in the paediatric population, the CHMP considered that the benefit-risk of suppositories containing terpenic derivatives in children less than 30 months is not positive under normal conditions of use.

2.5. Communication plan

As part of this referral procedure, the MAHs and the CHMP agreed the wording of a 'Dear healthcare professional' communication, common to all suppository products containing terpenic derivatives, designed to inform prescribers of the contraindications in children less than 30 months and in children with a history of epilepsy or febrile convulsion, to be sent to relevant health care professionals, including pharmacists.

2.6. Changes to the product information

The CHMP assessed the revised PI proposals submitted by the MAHs and noted extensive divergences. In particular, the minimum age recommendations varied from the neonatal period for some products, to 1 or even 6 months of age for others. Weight was not taken into account and age groups vary according to the composition of the suppository product, as did treatment duration without medical advice. Taking into account the risk of medication error related to age, the CHMP therefore considered that harmonisation was required for certain sections of the product information of suppositories containing terpenic derivatives.

The main changes, agreed by the CHMP and to be included as relevant in the PI of all suppositories containing terpenic derivatives, according to the intended age range of the product, were the introduction in Section 4.3 of contraindications in children less than 30 months because of the risk of neurological disorders, due to immaturity of the central nervous system, as well as in children with a history of febrile convulsion or epilepsy and in children with a recent history of anorectal lesion. These contraindications were also reflected in sections 4.2 and in the labelling and the package leaflet. In addition, the duration of use was limited to 3 days, due to risks related to terpenic derivatives storage in tissues and brain and the risk of rectal burning. A warning stating that the products are flammable and should not be approached to a naked flame was also added, together with a recommendation that the products should not be used in pregnant women and should not be used during breast-feeding.

3. Overall conclusion

In reaching its opinion, the CHMP took into account the totality of the available data on the safety of suppositories containing terpenic derivatives in paediatric populations, noting the limited efficacy data in the paediatric population, the absence of data on efficacy in children less than 30 months, the known neurological toxicity of terpenic derivatives, the risk of potentially severe neurological and local lesions and the risk of medication errors arising from the mistaken use of children formulations in infants.

The CHMP concluded that the data confirms the concerns that suppositories containing terpenic derivatives can induce neurological disorders, especially convulsions, in children less than 30 months.

These concerns are strengthened by the fact that no direct relationships could be established between the quantity of terpenic derivatives administered and the occurrence or severity of the adverse events. The clinical evidence shows that children less than 30 months are more prone to neurological disorders due to immaturity of the central nervous system, which results in a higher susceptibility to neurological toxicity. In addition, limited clinically relevant efficacy has been demonstrated in the paediatric population and no data on efficacy is available in children less than 30 months. The CHMP therefore concluded that the use of suppositories containing terpenic derivatives should be contraindicated in children less than 30 months, as well as in children with a history of epilepsy or febrile convulsion and in children with a recent history of anorectal lesion.

The CHMP was of the opinion that marketing authorisations with a wide approved age range should be varied to contraindicate use in children less than 30 months while marketing authorisations where the only approved age range is children less than 30 months should be revoked.

The MAHs and the CHMP also agreed on the wording of a 'Direct healthcare professional' communication, to inform prescribers on the above agreed contraindications to be sent to relevant health care professionals, including pharmacists.

The relevant sections of the summary of product characteristics, labelling and package leaflet are set out in Annex III to the opinion.

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.