ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE REVOCATION OR THE AMENDMENTS OF THE RELEVANT SECTIONS OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMA, AS APPLICABLE TAKING INTO CONSIDERATION THE AGE RANGE OF THE APPROVED POPULATION

Scientific conclusions

Overall summary of the scientific evaluation of suppositories containing terpenic derivatives (see Annex I).

Suppositories containing terpenic derivatives have been authorised through national procedures in Europe since the 1950s and are currently authorised and marketed in seven EU member states. The products are typically indicated for supportive treatment for benign (mild) acute bronchial disorders, particularly productive and non productive cough. Following a safety review completed in May 2010 by the French National Agency to investigate potential neurological risks, mainly represented by convulsions, suppositories containing terpenic derivatives (including camphor, cineole, niaouli, wild thyme, terpineol, terpine, citral, menthol and essential oils of pine needle, eucalyptus and turpentine) were contraindicated in France in children less than 30 months and in children with history of febrile convulsion or epilepsy. France subsequently submitted a notification on 27th October 2010, initiating a referral procedure under Article 31(2) of Directive 2001/83/EC, to assess the potential neurological risk and its impact on the benefit-risk of suppositories containing terpenic derivatives in children less than 30 months. The procedure started in November 2010.

The CHMP assessed the totality of the data submitted by the Marketing Authorisation Holders (MAHs).
In particular, the CHMP looked at data on suppositories containing camphor, cineole (eucalyptol) and menthol, niaouli, thymus vulgaris and cineole, citral, cineole (eucapyptol), pine essential oil and guaiacol, turpentine and pine essence. The CHMP also took into account the 2010 safety review conducted by the French National Agency.

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 and no studies focused on infants and children 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.

Changes to the product information (PI)

The CHMP assessed the revised PI proposals submitted by the MAHs. In particular, the minimum age recommendations varied from the neonatal period for some products, to 1 or even 6 months of age for others. In order to address these divergences and taking into account the risk of medication error related to age, the CHMP decided to harmonise certain sections of the product information texts. 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 due to the risk of neurological disorders, especially convulsions, as well as in children with a history of febrile convulsion or epilepsy and in children with a recent history of anorectal lesion. 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.

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.

Grounds for the revocation or for the amendment of relevant sections of the summaries of product characteristics, labelling and package leaflet of the marketing authorisations, as applicable taking into consideration the age range of the approved population.

Whereas

- The CHMP considered the totality of the available data, including the 2010 French safety review;
- The overall efficacy data is scarce in the paediatric population and absent in children less than 30 months. The overall therapeutic benefit was considered to be limited;
- Serious adverse drug reactions including neurological events, mainly convulsions, have been associated with the use of suppositories containing terpenic derivatives in children less than 30 months;
- The biological plausibility of increased neurological toxicity in children less than 30 months was considered to be established due to the to immaturity of the central nervous system which results in a higher susceptibility;
- No dose-ADR relationship could be established and the observed risk of neurological adverse events could not be adequately addressed by measures other than contraindications in this population;
- The CHMP concluded that the benefit-risk balance of suppositories containing terpenic derivatives in children less than 30 months is not positive under normal conditions of use and that their use should therefore be contraindicated in this age population 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 has recommended the revocation or the variation, as applicable taking into consideration the age range of the approved population, of the Marketing Authorisations for suppositories containing terpenic derivatives (see Annex I). The amendments to the relevant sections of the Summary of Product Characteristics, Labelling and Package Leaflet are set out in Annex III