Annex II

Scientific conclusions and grounds for revocation of the marketing authorisations

Scientific conclusions and grounds for revocation of the marketing authorisations

Overall summary of the scientific evaluation of Caustinerf arsenical, Yranicid arsenical and other associated names for topical use (see Annex I)

Caustinerf arsenical, Yranicid arsenical and other associated names for topical use are indicated in the painless topical devitalisation of the dental pulp. These products contain arsenous anhydride (arsenic trioxide) which is used for pulp cauterization (necrosis of the tooth pulp).

A literature review was performed by the Marketing Authorisations Holders (MAHs) (Septodont and A.T.O. Zizine) which revealed a potential of genotoxicity related to the use of arsenic trioxide. In parallel, new genotoxicity assays (Ames test and in vitro micronuleus test) were conducted by the MAH with dental paste extracts of Caustinerf arsenical and the results were positive in the in vitro micronuleus test only.

Based on this positive genotoxicity results (clastogenicity) the MAHs informed the Competent Authorities of a potential serious impact on the benefit risk balance of the products.

The MAH created in June 2013 an expert panel to characterise the risks and further assess the need for potential changes to the Marketing Authorisations (MAs) of the concerned product. The expert panel concluded that the benefit/risk of the product was negative.

The MAHs therefore applied for an USR to National Competent Authorities where the products are authorised, proposing to:

- restrict the indication to the second line use;
- introduce a contraindication in children, pregnant and lactating women;
- point out in the relevant SmPC section that the risk of carcinogenicity cannot be excluded and that there is a risk of necrosis of periodontal tissues.

The French National Competent Authority (NCA) considered that the modifications of the SmPC proposed by the MAHs were neither acceptable nor appropriate given the genotoxicity data provided and the recommendation of the expert panel.

The French NCA therefore referred the matter to the CHMP to give an opinion under Article 31 of Directive 2001/83/EC on whether the MAs of Caustinerf arsenical, Yranicid arsenical and other associated names for topical use products should be maintained, varied, suspended or revoked.

On 24 October 2013, the CHMP started a referral procedure for Caustinerf arsenical, Yranicid arsenical and other associated names for topical use.

In its assessment the CHMP considered all available data submitted by the MAHs as well as published literature and data available to the Member States.

Preclinical and clinical safety

The MAHs provided an extensive review of all available data from pre-clinical, clinical studies and post-marketing experience. The risk of genotoxicity including human fertility, foetal development and carcinogenicity induced by arsenic trioxide was reviewed.

A detailed analysis of the risks of clastogenicity or/and aneugenicity as those are recognised as a risk factor for cancer when impacting somatic cells, and teratogenicity, embryo-toxicity/spontaneous abortions and impaired male fertility, when impacting germinal cells.

The MAHs conducted in vitro testing to assess the genotoxicity of the product Caustinerf arsenical and provided the results of an extensive review performed by an expert in toxicology on the impact of arsenic compounds on somatic cells. Also, since no reproductive toxicity studies in animals were conducted with Caustinerf arsenical or Yranicid arsenical, the MAHs provided a brief review of available data in scientific literature regarding effects of inorganic arsenic on reproduction.

The CHMP concludes that arsenic trioxide:

- is genotoxic in vitro and in vivo in rodents (clastogenicity) which would not allow a safe level of use of arsenic trioxide for achieving active concentrations,
- is carcinogenic in humans as stated by the IARC (Group 1),
- has an impact on germinal cells and is reprotoxic in animals and humans,

The CHMP is of the view that the overall risk of cancer, early foetal loss and impact on fertility associated with the use of Caustinerf arsenical, Yranicid arsenical and other medicinal products cannot be ruled out and the risk minimisation measures proposed by the MAHs will not allow avoiding the impact on human fertility.

In addition, following a review of the whole marketing authorisation supportive dossier a new information was highlighted by the MAH with regards to the systemic passage of arsenic that cannot be excluded. The provided study demonstrated low but measurable systemic level of arsenic after dental use. The risk of carcinogenicity is established by the local or systemic passage of arsenic. The CHMP is of the view that the reported systemic exposure aggravates the earlier concern about the potential genotoxicity of the products.

The CHMP also considered the overview of cases reported submitted by the MAHs which compiles safety data from a Global Safety Database as well as published literature and data available to the Member states.

The MAHs did not recently conduct any clinical trial with arsenic trioxide in dental paste.

The CHMP acknowledges that:

- no clinical practice guideline endorses the use of arsenic dental paste,
- many cases of osteonecrosis, soft tissue and dental necrosis, bone fistula and gingival discoloration have been reported, which is considered as serious adverse effect, management of which is very complicated.
- the risk of necrosis to periodontal tissues is high in comparison to the other serious adverse events and the necrosis of periodontal tissues together with infectious complications remain a very serious known adverse effect, hard to treat and difficult to control despite the SmPC recommendations.

To further address the risks of carcinogenicity and tissue necrosis and in response to the outstanding issues expressed by the CHMP, the MAHs propose the following additional risk minimisation measures:

- amendments in the product information in sections 4.1, 4.2, 4.3, 4.4, 4.6, 4.8 and 5.3 of the SmPC:
    - to restrict the indication to the last line use i.e. in the situations when anaesthesia techniques are not available or not possible to use in the EU patients;

- to contra-indicate the use of the products in children, pregnant and lactating women;
- to reinforce the revised indication and local conditions, the sealing of the treated cavity in order to minimise direct leakage of the material and diffusion of the arsenic, the reduction of the exposure (3 days instead of 7 days) with close monitoring and warning of the occurrence of pain;

- Communication to Health Care Professionals concerning the instructions of use (via a dear Health Care Professional Communication and educational materials).
- A drug utilisation study (DUS) in order to verify the comprehension of the indication, the awareness of the safety concern, the minimisation measures in the SmPC in term of restriction of indication, the new caution related use of the product at different time (e.g. when the restricted indication is implemented/ 6 months after the implementation/ 18 months after the implementation).
- The monitoring and analysis of reported cases including a specific questionnaire to collect evidence of the indication of the product (use in second intention), sealing of the cavity and the duration of the application.

After considering the data available and the risk minimisation measures proposed by the MAHs, the CHMP is of the view that the risk of osteonecrosis, soft tissue and dental necrosis, bone fistula and gingival discoloration is highly difficult to minimise or avoid. Even in case of the best practice the necrotic adverse reactions cannot be ruled out due to the specifics of dental anatomy or accidental spillage.

In addition, the CHMP is of the view that the proposed measures to mitigate the risk of necrosis are not so different from the current recommendations and common knowledge on the conditions of use of the product and though the effectiveness of those current measures would not mitigate the risk associated with those products.

With regards to the proposed DUS, the CHMP is of the opinion that it would not be ethically acceptable to expose patients to arsenic trioxide for which an expert panel concluded that a genotoxic, reprotoxic and carcinogenic risks have been demonstrated.

Finally, with regards to the reduction of exposure from 7 to 3 days, the CHMP does not find this measures acceptable since half of the periodontal necrosis cases reported in post-marketing period occurred within 3 days.

The CHMP considers that this risk is unacceptable taking into account the estimated benefit of the product and the existing safer alternatives.

Efficacy

The efficacy of the product is based on the above-mentioned single small prospective non-comparative study dated 1969, which estimated the efficacy in painless devitalisation of pulp to be 88% under optimal circumstances of use.

The CHMP notes that:

- the efficacy was also high in case where it was not possible to place the product directly in contact with the pulp,
- a number of ADRs have reported a lack of effect.

The design of the study and the small number of subjects included did not allow a reliable assessment of the efficacy in a way to have a comparison with the current standard treatment. In addition, for

safety assessment, the CHMP noted that this short study does not confirm the absence of arsenic leakage, granulomas or decrease in bone density.

Finally the CHMP noted that no national, European and international guideline endorse the use of arsenic dental paste in clinical practice. Alternative techniques (such as several types of local/regional anesthesics, general anesthesia, gas for inhalation) may be available.

Overall conclusion

Having considered all available data from pre-clinical, clinical studies, published literature and post-marketing experience on Caustinerf arsenical, Yranicid arsenical and other associated names for topical use containing products provided by the MAHs in writing and during an Oral Explanation, the Committee considered that the use of Caustinerf arsenical, Yranicid arsenical and other associated names for topical use is associated with risks of carcinogenicity and serious necrosis adverse reactions sometimes with sequelae.

The Committee considered that the potential for genotoxic, carcinogenic and reprotoxic effects of the systemic exposure to arsenic trioxide combined with the lack of knowledge about the extent of systemic exposure from the dental use of the arsenic trioxide paste is not acceptable. In addition, the Committee is of the view that the risk of tissue necrosis cannot be ruled out even under the conditions of careful dental practice and the proposed SmPC recommendations.

Risk minimisation measures proposed by the MAH such as amendments to the product information (restriction for use, addition of contraindications in paediatric population and during pregnancy and lactation), communication material and a PASS were considered during the discussions. The CHMP is of the view that these risk minimisation measures would not be able to adequately reduce the risks associated to those products..

The review of the available efficacy data (including data which became available since the initial marketing authorisation), showed limited efficacy of Caustinerf arsenical, Yranicid arsenical and other associated names for topical use in its approved indication which does not translate in evidence of a benefit for patients in particular in the current context of the therapeutic strategy where the knowledge acquired in pulp's devitalisation and analgesia techniques has considerably improved, and where safer options are available.

The MAHs confirmed that all the available data have been provided and that they will not be able to provide any further data to demonstrate the clinical benefit of Caustinerf arsenical, Yranicid arsenical and other associated names for topical use containing products in local anaesthesia. The CHMP took in account the MAH's position.

Finally the CHMP noted that the current international consensus for the recognition of *'sufficient evidence in humans of the carcinogenicity'* of arsenic trioxide along with the strict limitation of arsenic trioxide in the drinking water does no longer support the use of arsenic trioxide within the therapeutic armamentarium.

The CHMP therefore concluded that the benefit-risk balance of Caustinerf arsenical, Yranicid arsenical and other associated names for topical use in the indication of *"painless topical devitalisation of the dental pulp"* is not favourable.

Therefore, the CHMP recommended the revocation of the marketing authorisations for the medicinal products referred to in Annex I.

Benefit –risk balance

The CHMP considered that Caustinerf arsenical, Yranicid arsenical and other associated names for topical use products are associated with potential risks of carcinogenicity, tissue necrosis and show a limited efficacy in their approved indication.

The CHMP considered the proposed changes by the MAHs in the Summary of Product Characteristics and Patient Leaflet to mitigate these risks and concluded that these risk minimisation measures would not be able to adequately reduce the risks of serious adverse reactions to a clinically acceptable level.

The CHMP therefore concluded that the benefit-risk balance of arsenic trioxide containing medicinal products is not favourable.

Grounds for revocation of the marketing authorisations of Caustinerf arsenical, Yranicid arsenical and associated names for topical use

Whereas,

- The CHMP considered the procedure under Article 31 of Directive 2001/83/EC for Caustinerf arsenical, Yranicid arsenical and other associated names for topical use (see Annex I).
- The CHMP considered the totality of the data available for Caustinerf arsenical, Yranicid arsenical and other associated names for topical use in relation to its genotoxicity and the risk of carcinogenicity. This included the MAHs' responses, data available to Member States and published literature which became available since the original marketing authorisations.
- The CHMP considered the genotoxicity of arsenic trioxide and that its use is associated with a potential risk of carcinogenicity and serious adverse reactions such as tissue necrosis sometimes leading to sequelae.
- The CHMP considered that the additional risk minimisation measures proposed by the Marketing Authorisation Holders would not be able to adequately reduce the risk of carcinogenicity and serious adverse reactions to a clinically acceptable level.
- The CHMP considered that the available efficacy data, including data which became available since the initial marketing authorisations of Caustinerf arsenical, Yranicid arsenical and other associated names for topical use in its approved indication, were limited.
- The CHMP took into account the MAH's position that all the available data have been provided and that there was no possibility to provide additional data for the demonstration of the clinical benefit of Caustinerf arsenical, Yranicid arsenical and associated names for topical use in the painless topical devitalisation of the dental pulp.
- The CHMP therefore concluded, in view of the available data, that the genotoxicity, the risk of carcinogenicity and tissue necrosis associated with the use of Caustinerf arsenical, Yranicid arsenical and associated names for topical use in the treatment of painless topical devitalisation of the dental pulp outweigh the limited benefits.

The CHMP, as a consequence, concluded that the risk-benefit balance for Caustinerf arsenical, Yranicid arsenical and associated names for topical use is not favourable.

Therefore, in accordance with Article 32 of Directive 2001/83/EC, the CHMP recommends the revocation of the marketing authorisations for all medicinal products referred to in Annex I pursuant to Article 116 of Directive 2001/83/EC.