EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 April 2014
EMA/CHMP/10350/2014

Assessment report

for Caustinerf arsenical/ Yranicid arsenical and other associated names for topical use

active substance: ephedrine hydrochloride, lidocaine and arsenous anhydride

Procedure number: EMEA/H/A-31/1382

Note

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

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Background information on the procedure

1. Referral of the matter to the CHMP

On 1st of August 2013, Septodont and A.T.O. Zizine (MAHs) sent an Urgent Safety Restriction (USR) to France, Estonia, Lithuania and Latvia given that new data were available regarding the genotoxic potential of the product Caustinerf arsenical. On 2nd of August 2013 France notified the MAHs of the refusal of the USR and its intention to initiate a European review in order to evaluate the benefit/risk balance of medicinal products containing ephedrine hydrochloride, lidocaine and arsenous anhydride for topical use. Therefore the CHMP was requested to give its opinion on whether the marketing authorisations for Caustinerf arsenical/ Yranicid arsenical and other associated names for topical use should be maintained, varied, suspended or revoked.

On 11 October 2013, France triggered a referral under Article 31 of Directive 2001/83/EC.

2. Scientific discussion

2.1. Introduction

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 micronucleus 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.

2.2. Pre-clinical and clinical aspects

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.

2.2.1. Safety

The MAHs were asked to submit all available data from pre-clinical, clinical studies and post-marketing experience and provided 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 provided an extensive review on preclinical, clinical and post-marketing literature data.

A. Pre-clinical data: genotoxicity assays

The MAH conducted in vitro testing to assess the genotoxicity of the product Caustinerf arsenical. In addition, the MAH provided the results of an extensive review performed by an expert in toxicology on the impact of arsenic compounds on somatic cells. Finally, 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.

a) genotoxicity in vitro testing

An Ames test and an in vitro micronucleus test in TK6 cells were performed with Caustinerf arsenical extracts.

The results were negative in the Ames test but in the in vitro micronucleus test in TK6 cells, Caustinerf arsenical extract induced a statistically, biologically and dose related increase of micronucleated cells.

Even though Caustinerf arsenical was shown as not mutagenic in the Ames test, its clastogenic / aneugenic potential *in vitro* was confirmed.

Based on the above, the CHMP concludes that Caustinerf arsenical and Yranicid arsenical and other associated names for topical use have genotoxic properties.

b) Risk of clastogenicity or/and aneugenicity when impacting somatic cells

Complementing the above-mentioned genotoxicity tests, the MAHs provided an extensive review on the impact of arsenic compounds on somatic cells considering preclinical, clinical and post-marketing data available in literature on arsenic.

The International Agency for Research on Cancer (IARC) recommendations and data such as the IARC monograph on arsenic and arsenic compounds (IARC, 2012) were also considered. Based on the data provided by the MAHs, arsenic trioxide shows a clastogenic potential in vitro and in vivo in rodents; based on data available in the scientific literature, the mechanism of the genotoxic effect induced by arsenic trioxide involves the production of oxidative DNA damages. These primary DNA damages are converted into chromosomal damage which were shown both in vitro and in vivo in chromosomal aberrations tests (micronucleus assays).

In addition, these genotoxic effects could be amplified by the inhibitory properties of DNA repair of arsenic trioxide and its metabolites.

It is noted that the International Agency for Research on Cancer (IARC) has published a monograph on arsenic and arsenic compounds in 2012, highlighting the carcinogenic potential of arsenic trioxide which is classified as human carcinogen (Group 1) with tumour promoting effects. The IARC has concluded that:

- there is sufficient evidence in humans for the carcinogenicity of mixed exposure to inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate. Inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate, cause cancer of the lung, urinary bladder, and skin. Also, a positive association has been observed between exposure to arsenic and inorganic arsenic compounds and cancer of the kidney, liver, and prostate.
- there is limited evidence in experimental animals for the carcinogenicity of sodium arsenate, gallium arsenide, arsenic trioxide, and trimethylarsine oxide.
- arsenic and inorganic arsenic compounds are carcinogenic to humans (as defined as 'Group 1').

In view of the above, the MAHs proposed to decrease the exposure of arsenic trioxide contained in Caustinerf arsenical/Yranicid arsenical to 1.5 µg/patient/day corresponding to the toxicological threshold concern (TTC) recommended by the EMA regarding genotoxic impurities (EMEA/CHMP/QWP/251344/2006[1]).

The dose recommended for Caustinerf arsenical and Yranicid arsenical and other associated names for topical use is as described in the SmPC: *"Apply a pellet of paste, the size of a pinhead (about 1 mm in diameter), not more than 10 mg, to the cavity floor, without exerting excessive pressure and starting from the walls".* Applied at doses averaging 10 mg, the dose corresponds to 3 mg of arsenious trioxide, 0.1 mg of ephedrine hydrochloride and 3 mg of lidocaine base.

Therefore, the concentration of arsenic trioxide would be decreased in Caustinerf arsenical /Yranicid arsenical from 3mg to 0,015 mg. With such a decrease of 200 fold, the efficacy of the preparation will be questionable, the safe level of use of arsenic trioxide being difficult to identify under these conditions.

In conclusion, the CHMP considers that:

- arsenic trioxide (as contained in Caustinerf arsenical and Yranicid arsenical) has genotoxic properties in vitro and in vivo in rodents,
- these genotoxic properties are associated with tumour promoting effects, and
- arsenic trioxide is classified as carcinogenic in humans as stated by the IARC (Group 1).

The CHMP is of the view that the risk of cancer associated with the use of Caustinerf arsenical and Yranicid arsenical cannot be excluded and a safe level of use of arsenic trioxide cannot be achieved at active concentrations.

c) Risk of teratogenicity, embryo-toxicity/spontaneous abortions and impaired male fertility, when impacting germinal cells

Clastogenicity or/and aneugenicity are recognised as a risk factors for cancer when impacting somatic cells, and teratogenicity, embryo-toxicity/spontaneous abortions and impaired male fertility, when impacting germinal cells.

No reprotoxicity studies in animals were conducted with Caustinerf arsenical or Yranicid arsenical and the MAHs provided a brief review of available data in scientific literature regarding effects of inorganic arsenic on reproduction. The results are presented in the table below.

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002903.pdf

Table 1: Results of the impact of arsenic in reproduction

Type of data	Results
Preclinical	Arsenic is a recognised reproductive toxicant in humans and induces malformations, especially neural tube defects, in laboratory animals (Wang et al., 2006). Early studies showed that murine malformations occurred only when a high dose of inorganic arsenic was given by intravenous or intraperitoneal injection in early gestation. Oral gavage of inorganic arsenic at maternally toxic doses caused reduced foetal body weight and increased resorption. Recently, arsenic reproductive and developmental toxicity has been studied in situations more similar to human exposures and using broader endpoints, such as behavioural changes and gene expression. For the general population, exposure to arsenic is mostly oral, particularly via drinking water, repeated and prolonged over time. In mice and rats, methylated or inorganic arsenic via drinking water or by repeated oral gavage induced male and female reproductive and developmental toxicities. Furthermore, at non-maternally toxic levels, inorganic arsenic given to pregnant dams via drinking water affected foetal brain development and postnatal behaviours (Wang et al., 2006[2]). Arsenic given by repeated oral gavage to pregnant mice and rats was not morphologically teratogenic (Wang et al., 2006). Arsenic is shown to be embryotoxic and teratogenic in experimental animals (Vahter, 2009[3]). Arsenic was also observed to be a transplacental carcinogen in mice (Boekelheide et al., 2012[4]).
Preclinical, clinical	Ecological studies have indicated associations between in utero and/or early life exposure to arsenic at high levels and increases in mortality from cancer, cardiovascular disease and respiratory disease. Additional data from epidemiologic studies suggest intermediate effects in early life that are related to risk of these and other outcomes in adulthood. Experimental animal studies largely support studies in humans, with strong evidence of transplacental carcinogenesis, atherosclerosis and respiratory disease, as well as insight into potential underlying mechanisms of arsenic's health effects (Farzan et al., 2013[5]).
Clinical	Clinical data have demonstrated that arsenic can cross placenta barrier (Vahter, 2009[3]). However the passage over the mammary gland is limited, with little arsenic excreted in breast milk (Vahter, 2009[3]). Clinical studies have also showed that increased frequency of spontaneous abortions was associated with

[2] Wang A, Holladay SD, Wolf DC, Ahmed SA, Robertson JL. Reproductive and developmental toxicity of arsenic in rodents: a review. Int J Toxicol. 2006 Sep-Oct;25(5):319-31
[3] Vahter M. Effects of arsenic on maternal and fetal health. Annu Rev Nutr. 2009;29:381-99. doi: 10.1146/annurev-nutr-080508-141102
[4] Boekelheide K, Blumberg B, Chapin RE, Cote I, Graziano JH, Janesick A, Lane R, Lillycrop K, Myatt L, States JC, Thayer KA, Waalkes MP, Rogers JM. Predicting later-life outcomes of early-life exposures. Environ Health Perspect. 2012 Oct;120(10):1353-61. doi: 10.1289/ehp.1204934. Epub 2012 Jun 6
[5] Farzan SF, Korrick S, Li Z, Enelow R, Gandolfi AJ, Madan J, Nadeau K, Karagas MR. In utero arsenic exposure and infant infection in a United States cohort: a prospective study. Environ Res. 2013, 126: 24-30.

	high levels of arsenic from water (Vahter, 2009[3]). Studies looking at the exposure of arsenic during early life showed that it results in an increase of liver, lung cancers during the 30's-40's period (Vahter, 2009[3]). Although the vast majority of studies to date concerning drinking water inorganic Arsenic (iAs) exposure and spontaneous loss have been cross-sectional or ecologic by design, and conducted among populations with very high exposures [>10ppb], the possibility for an increased risk for spontaneous pregnancy loss in association with low-moderate drinking water iAs exposure remains plausible and if true represents a critical public health importance (Bloom et al., 2010[6]).

The results above indicated that in animals, arsenic showed the following reprotoxic effects:

- neural tube defects,
- reduced foetal body weight and increased resorption,
- malformations,
- modified foetal brain development
- behavioural changes.

It can therefore be established that arsenic has an impact on germinal cells.

The CHMP concludes that arsenic trioxide is teratogenic in animals whilst acknowledging that these reprotoxic effects are relevant for humans.

B. Clinical data

The CHMP noted that the MAHs had proposed to restrict the indication to the second line use, introduce a contraindication in children, pregnant and lactating women and modify the appropriate sections of the SmPC to point out that the risk of carcinogenicity cannot be excluded and that there is a risk of necrosis of periodontal tissues. These risk minimisation measures were considered as not acceptable by the French NCA.

To support the second line use with the exclusion of children, pregnant and lactating women, the MAHs provided a literature review and overall summary of the preclinical, clinical and post-marketing data available for the Caustinerf arsenical, Yranicid arsenical and other associated names for topical use. The MAHs did not recently conduct any clinical trial with arsenic trioxide in dental paste.

The risk of genotoxicity including human fertility, foetal development and carcinogenicity induced by arsenic trioxide was reviewed.

a) Effect on fertility and development:

Arsenic trioxide is clastogenic. Studies concerning impact of inorganic arsenic on human fertility parameters, such as reproductive organ damage, sperm parameters, time to pregnancy are currently lacking. However, most of epidemiologic studies (cross-sectional, ecologic and prospective cohort) have reported association between arsenic exposure and foetal loss (spontaneous abortion and/or stillbirth), which support an impact on germinal cells (notably for the early spontaneous abortions). Therefore, the CHMP considers that an impact on germinal cells and thus on human fertility cannot be excluded.

[6] Bloom MS, Fitzgerald EF, Kim K, Neamtiu I, Gurzau ES. Spontaneous pregnancy loss in humans and exposure to arsenic in drinking water. Int J Hyg Environ Health. 2010 Nov;213(6):401-13. doi: 10.1016/j.ijheh.2010.09.001

In addition, in humans, ingested inorganic arsenic can cross the placenta and concentrations in cord blood are similar to those in maternal blood, exposing the foetus to the chemical/metabolites. Association between arsenic exposure and foetal loss (spontaneous abortion and/or stillbirth) reported in most of epidemiologic studies could also be due to inorganic arsenic impact on embryo/foetal development. Moreover, some studies (cf. studies reported in table 1 above) have suggested association between inorganic arsenic chronic exposure and low birth weight, neonatal mortality, postneonatal mortality, but this was not extensively investigated and studies have limitations (in design and exposure assessment).

The CHMP is of the view that the risk of early foetal loss and effects on fertility associated with the use of Caustinerf arsenical and Yranicid arsenical cannot be excluded.

To reduce those risks, the MAHs proposed to contraindicate Caustinerf arsenical/Yranicid arsenical during pregnancy. However, the CHMP is of the opinion that this measure would not allow to protect patient against early foetal loss (because pregnancies could be unknown at an early stage) and/or to prevent any impact on male/female fertility. The CHMP considers that these risks are unacceptable taking into account the estimated benefit of the product.

b) Carcinogenicity:

Following 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 (Marmasse 1962).

The initial assessment focused on general toxicity and not genotoxicity or carcinogenicity. In this context, Marmasse measured the arsenic quantity in two patients' urine and found "hundredth of milligram per day" meaning 10µg per day for three days after the application of 1 mg of radiolabeled arsenic trioxide during the devitalisation procedure. He concluded that a systemic passage occurred but the quantity was negligible in term of general toxicity. He also found all the rest of radiolabeled arsenic in the tooth structure after extraction (40% in the devitalising agent, 18% in the root and 28% in the crown).

The above mentioned study demonstrates low but measurable systemic level of arsenic after dental use. The risk of carcinogenicity is established by the local or systemic passage of arsenic. Based on the above, the CHMP therefore concludes that the hypothesis of a possible arsenical passage in the systemic circulation cannot be excluded.

A report of a toxicology expert provided by the MAH concluded that taking into account the cumulative nature of arsenic and the possible systemic diffusion from the application point, there can be a large excess of systemic exposure. The report further clarified that the local concentration of arsenic trioxide after application of Caustinerf arsenical/Yranicid arsenical, is largely in excess compared to clastogenic concentration reported in the scientific literature and the concentration determined in the in vitro micronucleus assay performed with Caustinerf arsenical preparation. The presence of arsenic trioxide in Caustinerf arsenical and Yranicid arsenical "presents a toxicological concern in terms of local and systemic mutagenic and carcinogenic human risk."

The CHMP also noted that no other relevant data to rule out the potential systemic leakage of the product have been produced by the MAHs.

Based on the current response of the MAHs the CHMP concludes that the systemic exposure seems plausible after dental use of the products. Since no new data to better describe the risk of periodontal damage nor to mitigate the risk of systemic exposure have been submitted by the MAH, the CHMP is of the opinion that the estimates of risk of carcinogenicity remain of concern and cannot be excluded in humans.

The CHMP also acknowledged that a conscientious evaluation by the practitioner of tooth conformation (closed apex) and periodontal tissues before arsenical paste application is required to avoid damages.

C. Post-marketing data

The CHMP 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 cumulative search performed on 4th of December 2013 in the MAHs' Global safety database retrieved 69 cases of which 14 were serious and 55 non serious.

a) Cases report overview

From the 69 cases (including 68 medically confirmed), 14 cases were serious including 9 literature reports without mention of the brand names and 55 were non serious cases. No fatal outcome was reported. These 69 cases corresponded to 94 adverse effects (AEs) among which the most impacted System organ classes (SOC) are as follows:

- the "General disorders and administration site conditions" SOC describes 64 adverse reactions including 48 reports of lack of effect (LOE), one case of necrosis, one case of administration site pain, one case of application site pain, one case of fatigue, seven cases of pain, one case of product taste abnormal, one case of pyrexia, one case of swelling and one case of tenderness;
- the "Musculoskeletal and connective tissue disorders" SOC describes 17 cases including 3 cases of arthritis, one case of bone fistula, 12 cases of osteonecrosis and one case of soft tissue necrosis;
- the "Gastrointestinal disorders" SOC describes 8 cases including one case of dental necrosis, one case of gastric ulcer, one case of gastritis, one case of gingival discoloration, one case of gingival pain, one case of tooth pulp hemorrhage and one case of toothache;
- the "Infection and infestations" SOC describes 5 cases including one case of alveolar osteitis, one case of dental fistula, one case of osteomyelitis, one case of osteomyelitis chronic and one case of pulpitis dental.

Conclusion:

Among the 94 reported AEs, approximately 50% (48 AEs) are lack of efficacy cases. This important rate could be related to a bad preparation of pulp cavity before applying arsenic trioxide paste which does not allow for an optimal efficacy. It should be noted though that arsenic trioxide paste comes with a number of operational standards (strict operating protocol, tightly-sealed intermediate restoration, patient scheduling) that need to be followed precisely in order to ensure efficacy and safety of the product.

Fifteen AEs of osteonecrosis, soft tissue and dental necrosis, bone fistula and gingival discoloration were reported and showed evidence of the highly toxic nature of arsenic compound and its potential collateral damage of the periodontal tissue.

Eight reported AEs of osteitis, osteomyelitis and pulpitis show the risk of infection as the necrotic tissue of pulp offers a substrate for bacteria to proliferate.

b) Osteonecrosis

18 cases of necrosis of periodontal tissue have been reported cumulatively including 14 serious cases.

The Preferred Terms (PT) and case distribution of these 28 AEs is detailed below:

Gum discoloration (one case), dental fistula (one case), necrosis (two cases), osteomyelitis chronic (one case), osteomyelitis (one case), alveolar osteitis (one case), pulpitis dental (one case), dental necrosis (one case), arthritis (three cases), bone fistula (one case), osteonecrosis (12 cases), soft tissue necrosis (one case), necrosis (two cases).

Most of the patients were under 40 years of age (nine out of 12 patients for which the information was available) and the treatment duration was consistent with the recommendations provided in the SmPC (eight out of nine patients for which the information was available, were treated for seven day or less). For the majority of patients which experienced an AE (10/14 patients for which the information was available), this was within less than seven days and the outcome was favourable but three patients recovered with sequelae.

The CHMP noted that the risk of osteonecrosis has been mainly observed under recommended treatment duration (based on the cumulative review, when the information was available, 88% of AEs occurred within 7 days following arsenic trioxide paste application). It is difficult to ensure the return of the patient within 7 days following arsenic trioxide paste application since the pain of the patient was relieved. Therefore some patients keep arsenic in their mouth for a period longer than 7 days and show arsenical flare-up.

The CHMP acknowledges that Caustinerf arsenical /Yranicid arsenical medicinal products need to be used thoroughly in order to ensure tightly-sealed intermediate restoration: caution should be exercised during cavity preparation to not perforate the floor of pulp chamber which could provide an easy and direct route for leakage of the material, a temporary cement of relatively soft consistency should cover the paste so as not to cause too much pressure, which could cause an arsenical “flare-up” (as mentioned section 4.2 of the SmPC).

Despite these precautions allowing a reduction of arsenic trioxide paste leakage, a risk of diffusion of the product is possible beyond the apex of the tooth which could cause necrosis of periodontal tissue.

In addition, the CHMP was of the view that the currently recommended dose seems imprecise in the SmPC (10mg i.e. about 1mm in diameter) and difficult to apply in practical use.

Thus, given the cases reported and the highly toxic nature of arsenic trioxide, its necrotic and corrosive effects and its ability to diffuse through hard-tissue barriers, the CHMP concluded that the relationship between Caustinerf arsenical /Yranicid arsenical and the occurrence of necrosis of periodontal tissue was confirmed.

To mitigate this risk, the MAHs proposed to amend the section 4.2 of the SmPC (e.g. reduction of the duration treatment and dose). However the CHMP considered that these measures would be insufficient to minimise the risk of periodontal tissue necrosis.

Conclusion:

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

The literature publications relative to the consequence of arsenic trioxide leakage on peridontal tissues or prolongated application indicate the potential toxicity of arsenic trioxide on periodontal tissues and alveolar bone.

The CHMP is of the view that the risk of periodontal tissue necrosis related to arsenic trioxide paste exists and in spite of many recommendations, is highly difficult to minimise or avoid. In addition, this serious AE is lengthy and complex to treat.

c) Special situations and populations

Carcinogenicity

No cases related to carcinogenicity identified in preclinical and clinical data have been reported. However the absence of carcinogenicity in the post-marketing period does not exclude carcinogenicity risk since cancers are considered to be multifactorial in origin, they could be developed after a long time of exposition and dentists are not involved in cancer treatment.

Misuse/off-label

One case of intentional overdose has been reported in context of suicide attempt describing severe signs of intoxication with gastro intestinal disorders, renal disorders, hematologic disorder and hemodynamic instability. The outcome of this case was favourable despite the significant amount of arsenic ingested.

Three others cases have been reported in the literature review provided by the MAHs (Przegl Lek, 2007; Kruszewska S, 1996). Among them, one had a fatal outcome following myocardial dysfunction and cardiovascular collapse. Those patients had ingested few grams of arsenic trioxide paste which corresponded to a half or a third of Caustinerf arsenical /Yranicid arsenical jar.

Pregnancy/breastfeeding

Two drug maternal exposures were reported without any information of the date of the pregnancy at the time to application of Caustinerf Arsenical in the dental cavity. No information of the outcome was provided.

Paediatric population

No cases were reported in children treated with Caustinerf arsenical /Yranicid arsenical.

Conclusion on safety

Based on the data from preclinical, clinical studies and post-marketing experience, the main safety concerns with Caustinerf arsenical, Yranicid arsenical and other associated names for topical use are the risk of cancer and tissue necrosis.

With regards to the genotoxic/carcinogenic effect, 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.

Therefore, 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. This risk appears unacceptable taking into account the estimated benefit of the product and the existing safer alternatives.

In addition, the CHMP is of the view that the reported systemic exposure aggravates the earlier concern about the potential genotoxicity of the products.

With regards to the clinical data, 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 CHMP is of the view that the risk of necrosis to periodontal tissues is high in comparison to the other serious adverse events. 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.

2.2.2. Efficacy

Caustinerf arsenical/Yranicid arsenical contain three active ingredients which are arsenic trioxide, ephedrine hydrochloride and lidocaine hydrochloride. Each ingredient has a specific role:

- Arsenic trioxide is a necrotising agent which gives the main effect of the product by killing the surrounding cells
- Ephedrine hydrochloride is a vasoconstriction agent. Local vasoconstriction in the pulp chamber prevents excessively rapid diffusion of the necrotizing active substance, arsenious trioxide. Vasoconstricting effect limits blood exchanges in the dental pulp, thus contributing to pulp devitalization.
- Lidocaine hydrochloride is an anaesthetic and relieves the pain.

A clinical study with three parts was performed by Professor ACHARD (1969) showing efficacy and has already been submitted in the regulatory dossier for the first approval and following national renewals. The study showed:

- A group of 50 patients with an acute or chronic pulpitis of one tooth was treated by application of the product in direct contact with the dental pulp, after removal of softened dentine using a bur then an excavator. The product was sealed in using a temporary occlusive dressing. All patients were evaluated three to five days after the treatment. In 88% of cases, the product was effective and caused virtually no pain after four to five days of close contact with the pulp.
- In a second group of 25 patients treated by an application of the product, it was not possible to place the product directly in contact with the pulp. Thus, a thin layer of dentine persisted between the product and the pulp. The product was covered with a fairly soft cement and was left in place for seven to ten consecutive days. Pain was reported in 32% cases before the treatment, in 4% during the treatment, in 12% during the removal of the radicular pulp and no case reported pain during the removal of the pulp from the chamber.
- In a third group of 14 patients, follow-up radiographs were taken six to 14 weeks after sealing of the root in order to evaluate the risk of arsenic leakage. No decrease in the density of the periapical bone nor evidence of granuloma formation were seen.

The clinician concluded that:

- the product provides adequate pulp devitalisation;
- the devitalisation is sometimes incomplete (some patients experienced mild pain in the apical portion of the root);
- the product is rarely responsible for painful reactions;
- no arsenic leakage occurred in this study;
- follow-up radiographs were in favour of arsenic therapy, with no granulomas or decrease in bone density;

- and recommended safety rules should be followed during use of arsenic:
    - it is imperative that a temporary tight coronary filling be placed over the product so as to prevent leakage of the active substances towards the gum and bone through the softened dentine;
    - it is imperative that the filling be placed so as to avoid compression on the pulpal wall, since this would cause pain;
    - it is imperative, when removing the dressing after no more than seven days, that a careful check be made to ensure that there is not the slightest trace of residual finished product. This is easily done since the product is blue.

Many alternative technique and products of pulp's devitalisation currently exists and are now recommended by European, national and international guidelines (such as European Society of Endodontics, 2006; HAS 2008; Carrotte 2004, National guidelines 2006, Faculty of dental surgery 2012; Cox 2004; Guide to clinical endodontics, 2002; Clinical Affairs Committee 2009; Abuabara 2012): several types of local/regional anaesthetics, general anaesthesia, gas for inhalation, etc.

Several literature data concluded that arsenical paste has no place in contemporary dental practice (cf. table 1).

Conclusion on 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.

3. Overall discussion and risk/benefit assessment

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.

4. 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.

Appendix 1

Divergent positions to CHMP opinion

Article 31 referral of Directive 2001/83/EC

Procedure No: EMEA/H/A-31/1382

Caustinerf arsenical/ Yranicid arsenical and other associated names for topical use

Divergent statement

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the suspension of a Marketing Authorisation for Caustinerf arsenical/Yranicid arsenical for the following indication:

Painless dental pulp removal

The reasons for divergent opinion were as follows:

No new (safety or efficacy) clinical data have been provided in this procedure that supports a change in the risk/benefit profile of Caustinerf arsenical/Yranicid arsenical in the approved indication. The identified risks have been well known in the EU for numerous years. With respect to carcinogenicity issues as a safety concern with respect to use of this product, the MAHs' justification that considering the short duration of use of this product, the urinary data from 2 patients show that the resultant arsenic levels are well below ICH limits for genotoxic impurities is plausible. The main documented reason to leakage issues arise because of incorrect cement application by dentists. A clinically relevant effect is well established as devitalising-pulp agent because arsenic has cytoxic effects. In the public domain, documented issues of necrosis of periodontal tissues have been resolved adequately following simple debridement.

With respect to use of the product, there is a potential use of the product with a subgroup of licensed dental practitioners who have been trained to use this product and where local anaesthetics do not work (phobia of injections by patients, delayed conduction pathways (due to modulation of sodium channels) and NSAIDs are contra-indicated. In addition pulpitis is an emergency condition and there is benefit for use of this product in this scenario. An additional benefit of this product is in a situation where the patient needs time to delay the subsequent intervention of root canal sealing. Although this product is not marketed in many EU countries, an alternative treatment to when this product is used (i.e. last line when anaesthesia is not possible) used in EU member states is dental extraction. This alternative option, however, might not be acceptable to patients and thus this medicinal product offers an alternative to dental extraction.

With respect to Risk Minimisation Measures, the MAH has proposed SmPC modifications including a restriction in indication to "painless devitalisation of the pulp in second intention when anaesthesia techniques are not accessible or if local anaesthesia does not work". The MAH has also proposed a PASS study to obtain more information on any adverse effects (including leakages with this product). However an additional Risk Minimisation Measure could be introduced to help support further the benefit-risk profile of this product i.e. restrict the promotion of this medicinal product as a topical devitalisation product as the technique to apply this product is not being thought any longer in the EU. The overall evidence on long-term safety for this product is sufficient and therefore the risk-benefit is positive if the above Risk-minimisation measures are introduced.

CHMP members expressing a divergent opinion:

John Joseph Borg (MT)	25 April 2014	Signature: .....
Dimitrios Kouvelas (GR)	25 April 2014	Signature: .....
Juris Pokrotnieks (LV)	25 April 2014	Signature: .....