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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR) Octenidine dihydrochloride (all mammalian food producing species)

On 8 February 2012 the European Commission adopted a Regulation¹ establishing maximum residue limits for octenidine dihydrochloride in all mammalian food producing species, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Octenidine dihydrochloride is intended for use in all mammalian food producing species for skin and mucosal disinfection and short-term supportive antiseptic wound treatment as a 0.1% aqueous solution for cutaneous use.

Schülke & Mayr GmbH submitted the application for the establishment of maximum residue limits to the European Medicines Agency, on 30 July 2009.

On 9 December 2009 the Committee for Medicinal Products for Veterinary Use adopted a list of questions to be addressed by the applicant. The response to the list of questions was submitted on 12 August 2010.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 8 February 2011 the establishment of maximum residue limits for octenidine dihydrochloride in all mammalian food producing species.

On 12 July 2011 the European Commission requested a reconsideration of the opinion of 8 February 2011 to review the possibility of extrapolation to poultry, eggs and honey.

On 15 September 2011 the Committee for Medicinal Products for Veterinary Use considered the Commission's request, reviewed the considerations with regard to extrapolations and confirmed the recommendation for the establishment of maximum residue limits for octenidine dihydrochloride in all mammalian food producing species.

Subsequently the Commission recommended on 23 December 2011 that maximum residue limits in all mammalian food producing species are established. This recommendation was confirmed on 13 January 2012 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 8 February 2012.

¹ Commission Regulation (EU) No 107/2012, O.J. L36, of 09.02.2012



European public MRL assessment report (EPMAR)

Octenidine dihydrochloride (all mammalian food producing species)

Summary of the scientific discussion for the establishment of MRLs

Substance name:	Octenidine dihydrochloride
Therapeutic class:	Anti-infective agents/Antiseptics
Procedure number:	EU/09/170/SCM
Applicant:	Schülke & Mayr GmbH
Target species:	All mammalian food producing species
Intended therapeutic indication:	Skin and mucosal disinfection and short-term antiseptic wound treatment
Route(s) of administration:	Cutaneous

1. Introduction

Octenidine dihydrochloride (N,N'-(1,1 0-Decandiyl-di-1 (4-H)-pyridinyl-4yliden)bis(1-octanamine)-dihydrochloride - CAS No 70775-75-6) is an antiseptic agent intended for use in all mammalian food producing species for skin and mucosal disinfection and short-term supportive antiseptic wound treatment as a 0.1% aqueous solution for cutaneous use.

Octenidine dihydrochloride has been used as an antiseptic agent in human medicine.

2. Scientific risk assessment

2.1. Safety assessment

2.1.1. Overview of pharmacological properties

Pharmacodynamic properties including mode of action

Octenidine dihydrochloride shows antiseptic activity against a wide range of bacteria and some fungus *in vitro*. The lowest MIC value (1 ppm) for octenidine dihydrochloride was observed for *Staphylococcus aureus*. Octenidine dihydrochloride showed a lower MIC value for the MRSA strains than other studied antiseptics. Cutaneous application of octenidine dihydrochloride on hands and feet of cynomolgus monkey reduced resident microflora on the skin. This reduction was dependent on concentration and number of applications.

No studies on secondary pharmacodynamics or pharmacodynamic drug interactions were submitted. This is despite the fact that cationic substances, like octenidine dihydrochloride, might react with anionic substances and thus impair the antiseptic effect. However, the lack of secondary pharmacodynamic and drug interaction studies was considered justified as no information on pharmacodynamic effects other than microbicidal effects can be found in the literature and pharmacokinetic studies with octenidine dihydrochloride indicate a low systemic exposure after cutaneous application.

Pharmacokinetic properties (mainly in laboratory animals)

Many of the pharmacokinetic studies performed for octenidine dihydrochloride are old with limited description and reporting. However, all studies both *in vitro* and *in vivo* show the same tendency, i.e. that octenidine dihydrochloride is poorly absorbed after cutaneous and oral administration. From a 14-day vaginal irritation study conducted in rabbit, and a study on the influence of a formulation containing 0.1% octenidine dihydrochloride and 2% phenoxyethanol on artificially induced skin lesions in rats it was reported that no octenidine dihydrochloride was detectable in serum, based on results of an analysis with a limit of detection of 40 ng/ml.

The elimination of the substance is mainly in the faeces and no accumulation in the body was observed. No metabolism studies have been performed.

2.1.2. Calculation of pharmacological ADI, if relevant

No pharmacological ADI has been calculated. This is considered acceptable as no relevant pharmacodynamic effects have been identified.

2.1.3. Overview of toxicology

Single-dose toxicity

Octenidine dihydrochloride was tested in single dose (non GLP) toxicity studies, at doses up to 3160 mg/kg orally in rat and up to 800 mg/kg orally in rabbit. Mortality was observed at 794 and 800 mg/kg respectively. Effects consisted mainly of dyspnoea, ataxia, inactivity, reduced motor activity, nasal discharge, stool changes, anorexia, hyperaemia of duodenum and hyperaemia and ulceration of the stomach and irritation of the gastrointestinal tract.

Repeated dose toxicity in mice

In an oral gavage subchronic study in mice with doses up to 256 mg/kg bw there was a high incidence of mortality and a second set of animals administered lower doses (0.5, 2.0 and 4.0 mg/kg bw) had to be initiated (part B, 13 weeks). In part B of this study no NOEL was identified. The low dose (0.5 mg/kg) was considered a LOEL as respiratory distress; gaseous distension and weight loss were seen. However, the weight loss was recovered by the end of week 2. One male and one female died in the low dose group and it was argued that these deaths were due to possible intubation error and acute stress; however there was no microscopic or macroscopic evidence of perforation. It was suggested that the gaseous distension observed in all dose groups was related to a change in gut flora induced by octenidine dihydrochloride, also leading to decreased metabolic efficiency with subsequent decrease in bodyweight gain. Swelling and gaseous distension is indeed a common finding following oral administration of antimicrobials. This may cause abdominal pressure against the diaphragm with subsequent respiratory distress. However, in part B of the study, mice showed signs of respiratory distress even at the low dose without corresponding gaseous distension. Macroscopic examination did not reveal any possible cause and no explanation for the respiratory distress was apparent. No particular target organ toxicity was observed.

In another study in mice, octenidine dihydrochloride was incorporated into the diet. Since no toxicokinetic data were provided the exposure of the animals is unknown and there are no pharmacokinetic data available relating to octenidine dihydrochloride administered via food. However, a calculation of achieved intake was performed. A NOAEL of 32 mg/kg was suggested. Taking other oral studies into consideration, this value seems rather high. Whether the high NOAEL is due to octenidine dihydrochloride binding to the food or whether the animals were not exposed to the drug

was not discussed. However, there is not considered to be any need to address this point further as the NOAEL seen in this study will not be critical for the determination of the ADI.

Repeated dose toxicity in rat

In a 5-week study in rats administered oral doses of 5, 10 and 20 ml/kg of 0.1% mouthwash 10 ml/kg was considered as the NOAEL based on a change in bodyweight in males. In a 12-month study the mortality was observed to be dose dependent with 4, 15 and 30 dead animals (out of 56) in dose groups of 2, 8 and 32 mg/kg, respectively. It was suggested that macroscopic and microscopic lung changes indicate the possibility of an incidental introduction of gavage material into the lungs. This possibility is acknowledged; however, since no deaths occurred in the control group, toxic effects of the compound cannot be excluded. No NOAEL could be established.

Repeated dose toxicity in dog

In dogs dosed orally for 5 weeks, some instances (2 out of 6 animals) of loose stools were observed at the low (1 mg/kg) and mid dose (6 mg/kg), while in the high dose group (18 mg/kg) emesis was observed in 5 of 6 animals and loose stools in 3 of 6 animals. No effects were seen in control animals and a treatment related effect can therefore not be excluded. A NOAEL could not be set for this study and 1 mg/kg is considered to be the LOEL. In a 12-month study dogs were dosed orally with 2, 6 and 18 mg/kg bw. Symptoms observed in the high dose group were weight loss, emesis, salivation and anorexia. In this group 1 male and 4 females died. A NOAEL of 6 mg/kg bw was set.

Reproductive toxicity, including developmental toxicity

Fertility and reproductive parameters studied in rat were normal and comparable in all groups. Octenidine dihydrochloride was well tolerated, except at the high dose (45 mg/kg) where abnormal head movements were observed within 15 minutes of treatment. No adverse events were seen on the course of pregnancy, litter parameters or embryotoxicity in rat. In addition, no external, visceral or skeletal changes were observed in rat or rabbit. In rabbit, the mid (7.5 mg/kg) and high doses (22.5 mg/kg) were poorly tolerated by does (with 8 and 7 deaths respectively, in these groups), which showed prostration, weakness, nasal mucous discharge, rales, dyspnoea and reduced food consumption. In these two groups the litter loss was higher than in controls. It was argued that this was probably due to the poor survival rates of does. No embryotoxic or teratogenic effects were attributed to treatment. The maternal NOAEL was 15 mg/kg in rat and 2.5 mg/kg in rabbit and the NOAEL for effects on pups was 45 mg/kg in rat and 22.5 mg/kg in rabbit.

Genotoxicity

In most of the performed studies octenidine dihydrochloride was evaluated for potential genotoxic effects as a single agent. In addition, a fixed combination product containing 0.1% octenidine dihydrochloride, was also tested in some genotoxicity assays. Pivotal genotoxicity studies were performed according to GLP.

Octenidine dihydrochloride, in the presence and absence of S9, was negative in Ames tests in Salmonella strains TA 98, TA 100, TA 1535, TA 1537, TA 1538 and TA102 using test concentrations up to 5 µg/plate. At concentrations of 5 µg/plate and higher, octenidine dihydrochloride was toxic to the bacteria. Octenidine dihydrochloride showed no genotoxic potential with respect to gene mutations in bacteria.

Octenidine dihydrochloride did not induce chromosomal aberrations in cultured Chinese hamster ovary cells or in human lymphocytes, with or without S9 activation. The genotoxicity of octenidine dihydrochloride was investigated *in vitro* in the Mouse Lymphoma TK locus assay in L5178Y cells. The

results were negative. To summarise, there is no evidence of genotoxic potential of octenidine dihydrochloride in the *in vitro* mammalian cell tests.

In an *in vivo* mammalian bone marrow erythrocyte micronucleus assay in male and female mice with a single oral dose of 32 mg/kg, octenidine dihydrochloride did not show genotoxic activity. The dose in the main test was based on a preliminary toxicity test in which toxic effects on the bone marrow were seen at high doses.

In conclusion, the genotoxicity of octenidine dihydrochloride has been adequately studied and the weight of evidence is sufficient to conclude that octenidine dihydrochloride is not genotoxic.

Carcinogenicity

Carcinogenicity studies have been performed in mouse (dermal, 18-month) and rat (oral, 24-month) with octenidine dihydrochloride.

In mice, dermal application of an aqueous solution of octenidine dihydrochloride (0.125% and 0.50%), was performed three times per week for 18 months. No increase in incidence of neoplastic tumours was seen in males. In females increased incidence of hepatic hemangioendothelioma (2 of 58 animals in the high dose group only) and lymphosarcoma infiltrating the vagina (2 of 58 animals in high dose group only) were noted. However, it is considered that the observed tumours were coincidental as their incidence was within the historical spontaneous control range. Thus, octenidine dihydrochloride did not induce tumours in mice after dermal application three times per week. However, the relevance of the study can be questioned since octenidine dihydrochloride was applied three times per week rather than daily for 18 months. In any case, the route of administration is not relevant for setting a toxicological ADI.

In rats, a 24-month carcinogenicity study was conducted with doses of 0.5, 2.0 and 8 mg/kg bw/day (50 animals per sex per group). Data revealed a dose-dependent increase in irritant effect in the lung, particularly in males (pulmonary oedema, congestion, haemorrhage and occasionally severe inflammation) and these lesions were severe enough in the high-dose group to have been the cause of an increased mortality. Survival rate in the highest dose group was 28 and 38% in males and females, respectively. In the other groups survival varied between 54 and 60%. In females, benign neoplasms were observed in the islet cells in 1 of 30 animals in the control group, 0 of 25 animals in 0.5 mg/kg bw/day group, 3 of 29 animals in the 2 mg/kg bw/day group and 5 of 19 animals in the 8 mg/kg bw/day group. A statistical difference was demonstrated between females in the control and the highest dose group ($p < 0.05$). No increase in tumour incidence was noted in males. Since the absorption of octenidine dihydrochloride is extremely low, a direct effect of the compound is unlikely. However, changes in gut bacteria are known to influence the incidence of endocrine tumours in rats, and changes of this type could have been caused by octenidine dihydrochloride. Octenidine dihydrochloride is not genotoxic but based on the presented data, it cannot be excluded that it possesses carcinogenic potential. Due to the low survival rate in this study the results are difficult to interpret, however, the NOAEL was considered to be 0.5 mg/kg bw/day based on the occurrence of benign neoplasms in the 2 mg/kg bw/day group.

Studies of other effects including immunotoxicity and neurotoxicity

Three studies in guinea pigs were performed to evaluate the sensitisation potential of octenidine dihydrochloride. The results showed no photosensitising, delayed contact sensitisation or skin sensitisation potential. Immunomodulatory potential was evaluated in a study where octenidine dihydrochloride was added to human whole blood, which was then stimulated with lipopolysaccharide from *Salmonella abortus equi*. The only effect seen was a dose dependent increase in platelet derived growth factor-AB (PDGF-AB), which could be associated with a positive effect on wound healing.

No specific studies on neurotoxicity were performed. There were no signs of neurotoxicity in other toxicity studies.

2.1.4. Calculation of the toxicological ADI or alternative limit

Results from two of the presented studies were considered as possible starting points for the calculation of a toxicological ADI. The 13-week repeated dose study in mice was the study with the lowest LOAEL of 0.5 mg/kg bw/day based on gaseous distension, respiratory distress and weight loss. The gaseous distension noted at all doses is a likely consequence of effects of octenidine dihydrochloride on the gastrointestinal flora. However, the design of the 13-week study in mice was not adequate to fully evaluate effects on the gastrointestinal flora, which would normally be further investigated through microbiological studies leading to the establishment of a microbiological ADI. In the case of octenidine dihydrochloride microbiological studies were performed but the data generated were not considered to be sufficiently robust and consequently no microbiological ADI could be established (see section 2.1.5 below). In view of the observed effects on the gastrointestinal tract (in mice and in dogs), the inadequate design of the study in relation to the detection of microbiological effects on the gastrointestinal tract, the microbiological activity of the substance and the absence of a microbiological ADI it is considered appropriate to use an additional uncertainty factor of four in the derivation of the toxicological ADI in order to ensure that microbiological effects on the gastrointestinal flora are adequately covered. Using the standard uncertainty factor of 100 to account for intra- and inter-species variation, as well as an uncertainty factor of 2 to account for the use of a LOAEL instead of a NOAEL, and a further factor of 4 to take account of the uncertainty with regards to microbiological effects results in a value of 0.625 µg/kg bw (37.5 µg/person).

The other possible starting point for the derivation of a toxicological ADI is the NOAEL of 0.5 mg/kg bw/day established in the rat carcinogenicity study. Using this NOAEL and the standard uncertainty factor of 100 as well as an additional uncertainty factor of 5 to account for the fact that cancer is a serious and irreversible endpoint, results in a value of 1 µg/kg bw (60 µg/person).

As the value derived from the 13-week study in mice is the lower of the two calculated values the toxicological ADI is therefore established as 0.625 µg/kg bw (37.5 µg/person).

2.1.5. Overview of microbiological properties of residues

A study was performed to determine the MIC of various test organisms. In the study 9 different species, relevant for the intestinal flora, were tested. The MIC_{calc} was calculated to be 0.16 µg/ml. The study was not performed according to the relevant guideline (VICH Topic GL36 – studies to evaluate the safety of residues of veterinary drugs in human food: general approach to establish a microbiological ADI, CVMP/VICH/467/03-FINAL-corr), since only one strain per genus was tested, and the MIC values are not considered robust enough to use for calculating a microbiological ADI. The results from the provided study do however show that intestinal bacteria seem to be very sensitive to octenidine dihydrochloride. Some data from other studies on octenidine dihydrochloride show that MIC values from different strains are similar. The data were from 100 clinical isolates of *Staphylococcus aureus*, which is not a relevant species for the gastrointestinal tract. Some preliminary data, without any study report, were also presented for *Klebsiella pneumoniae* and *E. coli* with similar results.

Calculation of microbiological ADI

Based on the data provided, a microbiological ADI could not be established as the data provided are not considered to be sufficiently robust. Calculations using the data available resulted in a value of 0.59 µg/kg/day (35.2 µg/person per day), which is considered to provide an estimation of the order of magnitude of the microbiological ADI.

2.1.6. Observations in humans

Octenidine dihydrochloride has been used in humans for a long time so many human observations and studies have been performed. In one study on patients with leg ulcers a formulation containing 0.1% octenidine dihydrochloride and 2% phenoxyethanol was applied topically for two weeks. No octenidine dihydrochloride could be detected in blood samples, indicating no absorption.

2.1.7. Findings of EU or international scientific bodies

No evaluations by other international committees were available.

2.1.8. Overall conclusions on the ADI

As detailed in section 2.1.2, the calculation of a pharmacological ADI was not considered necessary. A toxicological ADI of 0.625 µg/kg bw (37.5 µg/person) has been established, as detailed in section 2.1.4. While a microbiological ADI has not been established, relevant effects on the gastrointestinal flora have been considered in the derivation of the toxicological ADI.

The toxicological ADI is therefore established as the overall ADI.

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

Two *in vitro* studies were performed using skin from the target species. The skin absorption of octenidine dihydrochloride in a formulation containing 0.1% octenidine dihydrochloride and 2% phenoxyethanol was assessed in porcine, bovine, equine, feline and canine skin. For intact skin no absorption was detected. In skin with disrupted barriers absorption could be seen in the two species studied. For porcine skin it was calculated as 0.6% and for bovine udder skin as 2.7%.

In another *in vitro* study the uptake of octenidine dihydrochloride in porcine skin after topical treatment was investigated. The results show that octenidine dihydrochloride adheres only to the outer layer (100 µm) of porcine skin. From the applied amount 40.4% was recovered in untreated skin, 34.7% in scalded skin and 31.7% in scalded and singed skin.

2.2.2. Residue depletion studies

Following cutaneous application octenidine dihydrochloride is poorly absorbed and consequently no residue depletion studies have been provided. Conservative estimates of residues consumption have been performed and compared with the ADI, as detailed in section 3.3., below.

2.2.3. Monitoring or exposure data

No monitoring or exposure data other than that described elsewhere in this report are available.

2.2.4. Analytical method for monitoring of residues

No analytical method has been provided. This is justified by the fact that MRLs are not proposed for the substance.

2.2.5. Findings of EU or international scientific bodies

No evaluations by other international committees were available.

3. Risk management considerations

3.1. Potential effects on the microorganisms used for industrial food processing

No data have been provided in relation to potential effects on dairy products. A conservative estimate of the amount of residues that could occur in milk following use of octenidine dihydrochloride to treat a wounded udder indicates that residues in milk would be present at a maximum level of approximately 5.5 µg per litre, i.e. 0.0055 µg/ml (see section 3.3. below). While studies have shown that *Lactobacillus acidophilus*, for example, is highly sensitive to octenidine dihydrochloride, the MIC values derived (0.09 µg/ml in the case of *Lactobacillus acidophilus*) are at least an order of magnitude greater than the conservative estimate of residue levels in milk. Consequently, no negative effects for industrial food processing are expected as a result of the use of octenidine dihydrochloride.

3.2. Other relevant risk management considerations for the establishment of maximum residue limits

Octenidine dihydrochloride is intended for skin and mucosal disinfection and short-term supportive antiseptic wound treatment in all mammalian food producing species. As the substance will be administered on the skin and has been shown to be very poorly absorbed across intact skin and disrupted skin, residue levels in tissues will be very low. While residue data in target species have not been provided, conservative calculations have been performed to estimate possible levels of residues that could occur in food (see section 3.3. below).

Given the proposed indication, consideration has been given to the possibility that use of the substance on the teats of milk producing animals might result in direct contamination of milk as a result of transfer of residues from the skin of the teat into the milk during milking. However, standard farming practices should ensure that this will not happen:

- contamination would only occur if liquid traces of the octenidine dihydrochloride containing solution remained on the teat at the time of milking but in practice teat dips are applied after milking, ensuring that any residual solution will have dried long before the animal is next milked;
- modern milking machinery washes teats with water and dries teats prior to milking;
- where modern machinery is not used teats are wiped dry before milking.

The direct contamination of milk with octenidine dihydrochloride is therefore considered to represent an unrealistic scenario and is not considered further.

3.3. Elaboration of MRLs

In the sub-section below conservative estimates of possible levels of residues that could occur in food are provided. These demonstrate that the maximum consumer exposure to residues of octenidine dihydrochloride would be at a level equal to approximately 50% of the ADI.

Article 14(5) of Regulation (EC) No 470/2009 indicates that the establishment of MRLs is not required where these are not necessary for the protection of public health. Volume 8 of the Rules governing medicinal products in the European Union indicates that substances with poor absorption from sites of local application may be considered on their own merits to determine whether the establishment of MRLs is necessary. Given that data from in vitro studies with cattle, pig and horse skin indicate that cutaneously administered octenidine dihydrochloride is poorly absorbed across the skin and given that conservative estimates of consumer exposure to residues indicate that the maximum theoretical

consumer exposure arising from ingestion of tissues and milk would be at a level approximately equal to 50% of the ADI, the establishment of MRLs for octenidine dihydrochloride is not considered necessary for the protection of public health.

The conclusion that MRLs are not required for octenidine hydrochloride relates to cutaneous administration only and therefore the use of the substance should be restricted to cutaneous use.

Calculation of theoretical daily intake of residues

A conservative estimate of residue levels that could occur in tissues of target animals following treatment with octenidine dihydrochloride has been performed. The estimate is based on the assumptions that the highest concentration of octenidine dihydrochloride used is 0.1%, the maximum amount of product administered is 1.5 g/100 cm² (i.e. 1.5 mg octenidine dihydrochloride/100 cm²), 2% of the body area is treated and the absorption rate is 5% (*in vitro* data demonstrate that octenidine dihydrochloride was not absorbed across intact skin while absorption across disrupted skin was 2.7%). This would lead to a tissue concentration of 2.75 µg/kg in pigs, which was the species with the highest calculated residue levels.

In addition, as pig skin is included in the food basket residues retained in the skin of this species must also be taken into account. A conservative estimate of the amount of residues that could be ingested as a result of consuming pig skin was performed using the results of the *in vitro* skin uptake study, in which 31.7% of applied octenidine dihydrochloride was retained in skin that had been scalded and singed (see section 2.2.1 above). The calculation assumes a consumption of 50 g per day of porcine fat and skin in natural proportions, of which 10% consists of porcine skin. With an average thickness of 10 mm the outer layer forms 1% of the skin (the results of the *in vitro* skin uptake study showed that residues were retained only in the outermost 100 µm thick layer of skin). Taking the food basket portion into account 50 mg (0.05 g) of the outer layer of skin will be part of the total daily diet. After treatment of 100 cm² porcine skin 475.5 µg octenidine dihydrochloride was seen to adhere to the outer 100 µm layer of skin in the *in vitro* skin uptake study. As this amount of skin was seen to weigh 2.75 g, it can be concluded that consumption of 50 mg of the outer layer of skin would result in consumption of 8.6 µg octenidine dihydrochloride.

As octenidine dihydrochloride products might be used to treat wounds on the udder a conservative calculation has been performed to estimate the possible level of residues in milk that would result. In this calculation it is assumed that the skin surface of the udder is 1500 cm², and that the wounded portion of the udder corresponds to 10% of the surface (150 cm²). Octenidine dihydrochloride is applied at a dose of 1.5 mg/100 cm², i.e. 2.25 mg of octenidine dihydrochloride would be applied to the wounded area. As above, absorption is considered to be 5%, resulting in the potential absorption of 11.25 µg octenidine dihydrochloride, which would be distributed into a milk volume of 20 litres (the daily milk production). Based on this it is estimated that the consumer ingestion of residues of octenidine dihydrochloride in milk would correspond to 8.5 µg (in 1.5 litres milk).

Based on the above conservative estimates of residue levels in tissues (including porcine skin) and in milk, the consumer intake of residues of octenidine dihydrochloride resulting from consumption of the daily foodbasket can be calculated to be 18.5 µg/person (1.4 µg from 500 g of tissue, 8.6 µg from porcine skin, and 8.5 µg from milk). This provides a margin of safety of greater than 2 in relation to the overall ADI.

3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EU) No 470/2009 the CVMP considered the possibility of extrapolating the recommendation for the establishment of maximum residue limits for octenidine dihydrochloride based on *in vitro* data with some mammalian skin species to other food producing species and food commodities. Taking into account the current scientific knowledge the recommendations on extrapolation are justified as follows:

Animal species/food commodities	Extrapolation possible (YES/NO)	Justification
Poultry (including eggs)	No	<p>The level of skin absorption could not be estimated as the skin structure of poultry differs considerably from pigs and no data on residues in/on poultry skin were available to allow consumer exposure to be estimated.</p> <p>The available data are therefore not sufficient to allow adequate evaluation of the risk to consumer safety posed by residues in poultry tissues in particular skin which for pigs and poultry is considered residues target tissue (skin and fat).</p>
Fin fish	No	<p>The substance is presented as an aqueous solution for disinfection of the skin and the safety of residues evaluation based on poor absorption across the skin in mammals. The possibility of adding the substance to the water (waterborne bath) would represent a significant different mode of application and exposure for which no data were available allowing an adequate evaluation of the risk to consumer safety.</p>
Honey	No	<p>Residue depletion in honey does not occur through metabolism and consequently conclusions drawn from data on residues in other food products cannot be extrapolated to honey. The available data are not sufficient to allow adequate evaluation of the risk to consumer safety posed by residues in honey.</p>

3.5. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- the limited pharmacokinetic data available indicate that octenidine dihydrochloride is not absorbed through intact skin and absorbed only to a very limited extent through abraded skin;
- the toxicological ADI of 37.5 µg/person was established as the overall ADI;
- octenidine is intended for cutaneous use only;
- conservative calculations indicate that consumer exposure to residues resulting from the ingestion of tissues (including skin) of animals administered octenidine dihydrochloride to the skin will be substantially below the ADI;

the CVMP recommends the inclusion of octenidine dihydrochloride in table 1 of Regulation (EC) No. 37/2010 in accordance with the following table:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Octenidine dihydrochloride	Not applicable	All mammalian food producing species	No MRL required	Not applicable	For cutaneous use only	Anti-infectious agents/ Antiseptics

4. Background information on the procedure

Submission of the dossier:	30 July 2009
Steps taken for assessment of the substance	
Application validated:	11 August 2009
Clock started:	12 August 2009
List of questions adopted:	09 December 2009
Consolidated response to list of questions submitted:	12 August 2010
Clock re-started:	13 August 2010
Decision on need for an oral hearing:	13 October 2010
Oral hearing:	12 January 2011
CVMP opinion adopted:	8 February 2011
Request for reconsideration from the Commission:	12 July 2011
Revised C VMP opinion adopted:	15 September 2011