

1. Name of medicinal product (if available – number of registration certificate):	Septolete® total with lemon and ginger flavor 3 mg/1 mg lozenges (benzylamine hydrochloride 3 mg / cetylpyridinium chloride 1 mg)
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1) the type of medicinal product for which the registration was made or planned

2) the undertaken study:

☐ yes ☐ no if not explain

Salmonella typhimurium Reverse Mutation Assay of Benzydamine HCl

2. Pharmacology:

On the markets worldwide, there are many preparations for self-medication of mouth and throat infections, which contain cetylpyridinium chloride and benzydamine alone or in combination. Long-term therapeutic use and post-marketing experience shows that lozenges with cetylpyridinium chloride and benzydamine are safe and effective drugs for relieving the symptoms associated with mouth and throat infections. Also the data from clinical studies and pharmacovigilance have confirmed that the combination has a good safety and efficacy profile. The results obtained in non-clinical and clinical studies have been summarized in Module 2.4 “Non-clinical overview”. The copies from the published scientific literature that were used for Module 2.4 are enclosed with Module 4. Taking into consideration the above, it is not necessary to tabulate and summarize all the results found in the literature in Module 2.6. “Non-clinical summary”. Medicinal products which contain combination of cetylpyridinium chloride and benzydamine have a well established medical use, recognized efficacy and an acceptable level of safety. This statement is supported by the document published by the European Commission in June 2004: Questions and Answers. The rules governing medicinal products in

the European Union, Volume 2, Notice to Applicants, Volume 2B: Presentation and content of the dossier Common Technical Document (CTD) 2003 Edition, Update June 2004; Question/Answer 13.

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|---------------------------------|---|
| 1) primary pharmacodynamics | / |
| 2) secondary pharmacodynamics | / |
| 3) safety pharmacology | / |
| 4) pharmacodynamic interactions | / |

3. Pharmacokinetics:

On the markets worldwide, there are many preparations for self-medication of mouth and throat infections, which contain cetylpyridinium chloride and benzydamine alone or in combination. Long-term therapeutic use and post-marketing experience shows that lozenges with cetylpyridinium chloride and benzydamine are safe and effective drugs for relieving the symptoms associated with mouth and throat infections. Also the data from clinical studies and pharmacovigilance have confirmed that the combination has a good safety and efficacy profile. The results obtained in non-clinical and clinical studies have been summarized in Module 2.4 "Non-clinical overview". The copies from the published scientific literature that were used for Module 2.4 are enclosed with Module 4. Taking into consideration the above, it is not necessary to tabulate and summarize all the results found in the literature in Module 2.6. "Non-clinical summary". Medicinal products which contain combination of cetylpyridinium chloride and benzydamine have a well established medical use, recognized efficacy and an acceptable level of safety. This statement is supported by the document published by the European Commission in June 2004: Questions and Answers. The rules governing medicinal products in the European Union, Volume 2, Notice to Applicants, Volume 2B: Presentation and content of the dossier Common Technical Document (CTD) 2003 Edition, Update June 2004; Question/Answer 13.

1) analytical methods and reports concerning their validation

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|-----------------|---|
| 2) absorption | / |
| 3) distribution | / |
| 4) metabolism | / |
| 5) excretion | / |

6) pharmacokinetic interactions (preclinical) /

7) other pharmacokinetic studies /

4. Toxicology:

1) single-dose toxicity /

2) toxicity in case of repeated injections /

3) genotoxicity:
in vitro

Ames test performed in *S. typhimurium* strains TA97a, TA98, TA100, TA1535 and TA102 with Benzydamine HCl revealed no significant mutagenic activity. The results obtained from this study have been summarized and tabulated in Module 2.6. "Non-clinical summary".

In vitro Bacterial Reverse Mutation Test (OECD No.471) was performed in *S. typhimurium* strains TA97a, TA98, TA100, TA1535 and TA102 with Benzydamine HCl in the presence or absence of metabolic activation and with and without preincubation conditions. Benzydamine HCl revealed no significant mutagenic activity.

in vivo (including additional toxicokinetic assessment) /

4) carcinogenicity: /

long-term studies

short-term or medium-term studies

additional research

5) reproductive toxicity and toxic effects on offspring development: /

impact on fertility and early embryonic development

embryotoxicity

prenatal and postnatal toxicity

studies in which the medicine is administered to offspring (non-mature animals) and/or evaluated for long-term effects

6) local tolerability /

7) additional toxicity studies: /

antigenicity (antibody formation)

immunotoxicity

study of mechanisms of action

drug dependence

metabolite toxicity

toxicity of impurities

other

5. Conclusions on preclinical study

Ames test performed in *S. typhimurium* strains TA97a, TA98, TA100, TA1535 and TA102 with Benzydamine HCl revealed no significant mutagenic activity. The results obtained from this study have been summarized and tabulated in Module 2.6. "Non-clinical summary".

The test item did not induced increase of the number of revertants in the absence and in the presence of metabolic activation in *Salmonella typhimurium* strains TA97a, TA98, TA100, TA1535 and TA102. Results of the additional test on the TA98 showed absence of revertants' increase which confirm that test item was not mutagenic for TA98 strain. Standard mutagens used as positive control of test system induced statistically significant increase of the number of revertants

under the same experimental conditions as applied for test item. On the basis of these results it was concluded that benzydamine HCl is not mutagenic for bacterial *Salmonella typhimurium* strains, under the experimental conditions described in this report.

Applicant (holder of
registration
certificate)


(signature)

JANJA DECELJ
(Name)



KRKA,
tovarna zdravil, d.d.,
Nova mesto

2021