Clinical Evaluation: **Product: Viruzyme Family**

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Signed: 

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1. SUMMARY:

This Clinical Evaluation Report dated 22.2.21 updates previous Clinical Evaluation Reports.

The Viruzyme range of products are designed to remove organic substances such as blood, mucous, and other tissues from surgical instruments prior to further processing such as disinfection and cleaning. They are also useful in removing biofilms which can harbour organisms which are particularly resistant to antibacterial agents. Viruzyme main users are technicians based in hospital sterilisation and endoscopy departments.

Their formulations are based on various enzymes and detergents. They can be varied slightly according to rinse water types and degree of foaming required.

In either case the Viruzyme range are low risk as they have no patient contact or user contact (providing the user uses protective gloves as indicated in the instructions and labels) and are generally a precursor to further procedures such as disinfection or sterilisation.

There are numerous similar products on the market and the Viruzyme range have been on the market for 5 years without complaint or report of any serious incidents.

The cleaning process is validated by visual inspection by the user and by a range of tests carried out by the manufacturer. There are no special hazards or precautions other than those listed on the labels and instructions for use.

In view of the above, this Clinical Evaluation is carried out ensure the Viruzyme range complies with ANNEX I of MDD/93/42/EEC by:

1. Risk assessment.
2. Process and product validation.
3. Comparison with equivalent products for technical and safety but not clinical (there is no clinical application to the patient).
4. A cursory consideration of the literature for adverse events and brief literature review (2016-20).
5. Compliance with the relevant harmonised Standards and other relevant Standards which are listed in the document AMITY/TD-VZF-5.2.

We therefore conclude that the objective of this clinical evaluation is to confirm the Viruzyme range of products comply with the Essential Requirements (MDD ANNEX I) by satisfactory compliance with the steps 1-5 listed above.

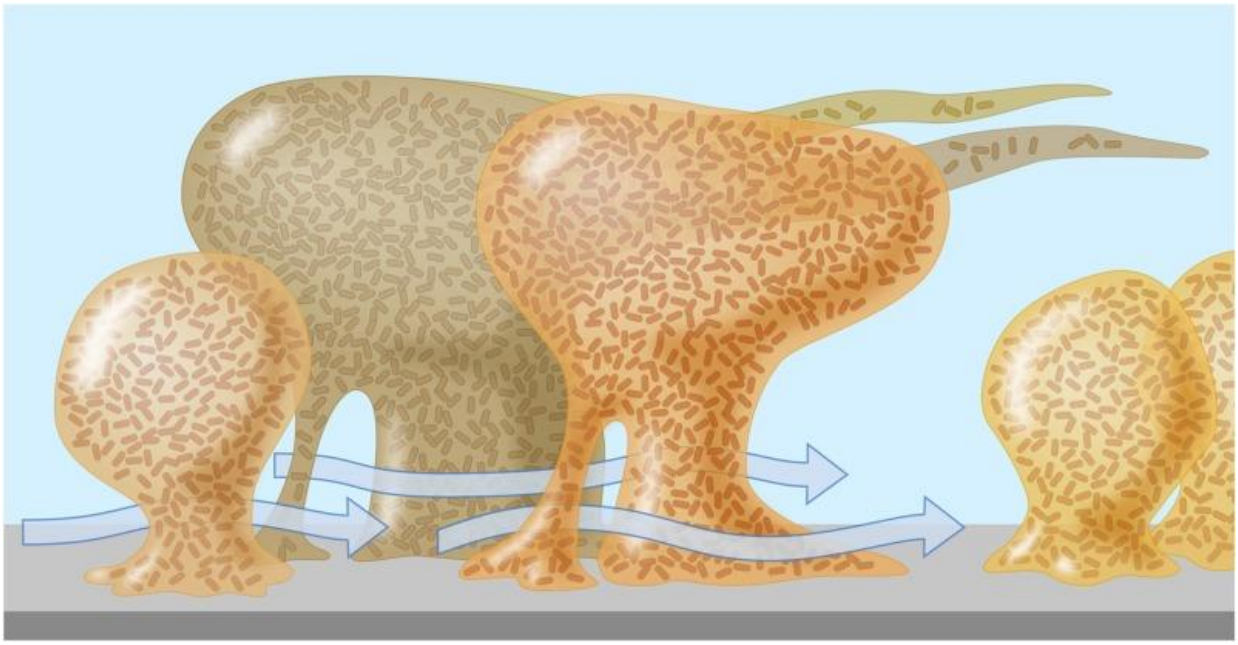
2. INTRODUCTION.

It is generally accepted that infection can be transferred from surgical instruments to patients if proper cleaning and subsequent disinfection or sterilisation processes have not been carried out efficiently. This is important especially with endoscopes where multiple channels can make effective cleaning more difficult.

Cleaning is the removal of visible soil (e.g., organic and inorganic material) from objects such as surgical instruments and surfaces and normally is accomplished manually or mechanically using water with detergents or enzymatic products, often accompanied by brushing. A cleaning process can be sufficient for items coming in to contact with healthy intact skin or not in contact with the patient. However, thorough cleaning is essential before high-level disinfection and sterilization because inorganic and organic materials that remain on the surfaces of instruments can interfere with the effectiveness of these processes.

BIOFILM.

A typical biofilm will contain around 85% polymeric substances and only 15% bacterial mass, and cells are located in matrix-enclosed “towers” and “mushrooms”. See diagram below:



Biofilms may form on different surfaces, including living or dead tissues, medical devices, water supply systems, or endoscope channels. Biofilm formation by microorganisms on inert surfaces has been extensively studied, and there is a direct relationship between the ability of the organism to form a biofilm and its pathogenicity.

Microorganisms in biofilms are protected from the host immune system and may be 1,000 times more resistant to antibiotics than normal surfaced based cells. The increased resistance to antimicrobial agents can be explained by poor penetration of an antibiotic into a biofilm, low growth rate, and formation of resistant phenotypes of microorganisms within biofilms.

Modern flexible endoscopes contain multiple channels and ports which can easily collect organic material and form biofilms which means the endoscope is more difficult to clean and decontaminate. This underlines the importance of thorough manual cleaning and the use of cleaning agents capable of breaking down the biofilm (such as Viruzyme) thus making it easier for the high level decontaminant agent to kill the remaining exposed organisms.

Condition to be treated.

The main claim for the Viruzyme range is that the solutions are intended for manual cleaning or soaking of surgical instruments and hard surfaces and are especially suited for use in the precleaning of flexible and rigid endoscope devices but can also be used to decontaminate other reusable medical devices.

Contra-indications.

The Viruzyme range are designed for initial cleaning of surgical instruments and hard surfaces. They should not be used to disinfect or sterilise surgical instruments or hard surfaces.

Precautions.

Some of the materials used in the Viruzyme family of products are hazardous by nature and could pose a safety threat to users such as NHS hospital staff responsible for cleaning and disinfecting medical devices such as endoscopes. Their protection is afforded by the issue of Safety Data Sheets to all potential users.

The Amity Viruzyme family of products should only be used as indicated on the product labels and instructions for use.

Clinical data to be considered.

As mentioned in the summary. A review of clinical data will be limited to identification of any adverse events or incidents due to lack of performance of similar cleaning agents.

See section 4.

3. PRODUCT DESCRIPTION AND RANGE.

See AMI-TD-VZF-1-1 Rev 001.

4. PRODUCT LITERATURE.

A description of the Viruzyme range can be seen on the Amity web site:

https://www.amityinternational.com/products/enzymatic-cleaners/

A list of competitive devices can be seen at the following web sites:

https://www.drweigert.com/com/products-system-solutions/neodisher-medical-laboratory

https://www.schumacher-online.com/en/

https://www.drdeppe.de/en/products/

https://www.borer.ch/en/products/borer-medical/

https://www.serchem.com/healthcare

https://www.steris.com/healthcare/products
https://www.medisafeinternational.com/product/3e-zyme/

https://www.alkapharm.co.uk/

https://www.bbraun.com/content/dam/catalog/bbraun/bbraunProductCatalog/S/AEM2015/en-01/b3/instruments-rangebrochure50000217.pdf

https://www.getinge.com/uk/product-catalog/detergents/

https://www.cantelmedical.eu/product/high-level-disinfectants/ https://www.cantelmedical.eu/product/detergent-decontaminant/

5. EQUIVALENT DEVICES.

Although equivalence is not claimed as part of the Viruzyme compliance to the MDD/93/42/EEC Annex I, Essential Requirements (see summary) it is prudent to list the most relevant competitors to the Viruzyme range to demonstrate how accepted these products are in the market, most of which show CE marks on their labels.

AMITY DEVICE	COMPETITOR DEVICE
Viruzyme VE protease, amylase, lipase, cellulose & mannanase enzymes	Borer.ch Prozyme active neutral multi-enzymatic concentrated detergent Dr Weigert neodisher Mediclean forte Dr Schumacher Thermoton Autozyme
Viruzyme V	Neodisher

five enzymes, protease, amylase, cellulase and mannanase and synergistic surfactants that have added safety	InstruZym 4 enzymes plus surfactants Dr Weigert neodisher SystemAct Steris – Polystica Ultra Concentrate Enzyme Dr Schumacher Multizyme Forte
Amzyme 3 Manual protolytic, amylase and lipase enzymes	Serchem.com Manual-Active8 Concentrated Manual Enzymatic Detergent. Dr Weigert neodisher Medizym Aniosyme DLT Plus Getinge Renuzyme WR
Amzyme 3 protolytic, amylase and lipase enzymes, complexing and sequestering agents, detergents and corrosion inhibitors	Neodisher MediZym enzymes and surfactants. Borer – Deconex Power Zyme Dr Weigert neodisher Mediclean Ecolab Solid Enzyme Detergent Aniosyme DLM Getinge Powercon Triple Enzyme Det Conc

6. LITERATURE REVIEW – PUBMED AND ADVERSE EVENTS.

6.1 Pubmed:

2016

“enzyme biofilm removal”

6.1.1

Antimicrob Agents Chemother
. 2016 May 23;60(6):3647-52.
doi: 10.1128/AAC.00400-16. Print 2016 Jun.
Enzymes Enhance Biofilm Removal Efficiency of Cleaners

Full text at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4879406/

Abstract

Efficient removal of biofilms from medical devices is a big challenge in health care to avoid hospital-acquired infections, especially from delicate devices like flexible endoscopes, which cannot be reprocessed using harsh chemicals or high temperatures. Therefore, milder solutions such as enzymatic cleaners have to be used, which need to be carefully developed to ensure efficacious performance. In vitro biofilm in a 96-well-plate system was used to select and optimize the formulation of novel enzymatic cleaners. Removal of the biofilm was quantified by crystal violet staining, while the disinfecting properties were evaluated by a

BacTiter-Glo assay. The biofilm removal efficacy of the selected cleaner was further tested by using European standard (EN) for endoscope cleaning EN ISO 15883, and removal of artificial blood soil was investigated by treating TOSI (Test Object Surgical Instrument) cleaning indicators. Using the process described here, a novel enzymatic endoscope cleaner was developed, which removed 95% of Staphylococcus aureus and 90% of Pseudomonas aeruginosa biofilms in the 96-well plate system. With a >99% reduction of CFU and a >90% reduction of extracellular polymeric substances, this cleaner enabled subsequent complete disinfection and fulfilled acceptance criteria of EN ISO 15883. Furthermore, it efficiently removed blood soil and significantly outperformed comparable commercial products. The cleaning performance was stable even after storage of the cleaner for 6 months. It was demonstrated that incorporation of appropriate enzymes into the cleaner enhanced performance significantly.

EVALUATORS CONCLUSION

This article has been rated at 8/10 as it conforms the efficacy of enzymatic cleaners in removing biofilms and in particular refers to an equivalent device to Viruzyme from Borer Chemie.

6.1.2

Polymers (Basel)
. 2020 Dec 17;12(12):3032.
doi: 10.3390/polym12123032.
Efficient Biofilms Eradication by Enzymatic-Cocktail of Pancreatic Protease Type-I and Bacterial α-Amylase

Full article at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7766206/

Abstract
Removal of biofilms is extremely pivotal in environmental and medicinal fields. Therefore, reporting the new-enzymes and their combinations for dispersal of infectious biofilms can be extremely critical. Herein, for the first time, we accessed the enzyme “protease from bovine pancreas type-I (PtI)” for anti-biofilm properties. We further investigated the anti-biofilm potential of PtI in combination with α-amylase from Bacillus sp. (αA). PtI showed a very significant biofilm inhibition effect (86.5%, 88.4%, and 67%) and biofilm prevention effect (66%, 64%, and 70%), against the E. coli, S. aureus, and MRSA, respectively. However, the new enzyme combination (Ec-PtI+αA) exhibited biofilm inhibition effect (78%, 90%, and 93%) and a biofilm prevention effect (44%, 51%, and 77%) against E. coli, S. aureus, and MRSA, respectively. The studied enzymes were found not to be anti-bacterial against the E. coli, S. aureus, and MRSA. In summary, the PtI exhibited significant anti-biofilm effects against S. aureus, MRSA, and E. coli. Ec-PtI+αA exhibited enhancement of the anti-biofilm effects against S. aureus and MRSA biofilms. Therefore, this study revealed that this Ec-PtI+αA enzymatic system can be extremely vital for the treatment of biofilm complications resulting from E. coli, S. aureus, and MRSA.

EVALUATORS CONCLUSION

This article has been rated at 7/10 as it confirms the efficacy of enzymatic cleaners in removing biofilms but suggests certain enzymes have specific activity against certain bacteria within biofilms.

6.1.3

Int J Food Microbiol
. 2021 Jan 2;336:108897.
doi: 10.1016/j.ijfoodmicro.2020.108897. Epub 2020 Oct 9.
Efficacy of flavourzyme against Salmonella Typhimurium, Escherichia coli, and Pseudomonas aeruginosa biofilms on food-contact surfaces

Abstract

Food contamination is a major public health concern, with Salmonella Typhimurium, Escherichia coli, and Pseudomonas aeruginosa being the prominent causal agents. They often produce resistant shields in food through biofilm formation and are difficult to remove from food-contact surfaces using conventional cleaning agents. In the current study, we investigated the efficacy of flavourzyme, an industrial peptidase, in biofilm removal from ultra-high molecular weight polyethylene (UHMWPE) and rubber surfaces and compared the corresponding efficacies with those of the commonly used DNase I. We noticed a significant reduction of young (24-h-old) and mature (72-h-old) biofilms on both surfaces after treatment with flavourzyme. The overall reduction potentiality of flavourzyme was higher than that of DNase I. The flavourzyme-mediated removal of biofilms appears to be caused by the gradual disruption of amide (NH) and polysaccharide (C-O-C) stretching bands of the extracellular polymeric substances (EPS) released by the microbes. EPS elimination and the cell-friendly behavior of flavourzyme were further confirmed by field emission scanning electron microscopy. Based on these findings, we suggest that flavourzyme can reduce microbial EPS formation, thus possibly controlling microbial food contamination. This finding reveals a new opportunity for the development of a novel method for controlling foodborne illness as well as food spoilage.

EVALUATORS CONCLUSION

This article has been rated at 6/10 as it confirms the efficacy of enzymatic cleaners in removing biofilms but suggests flavourzyme has specific activity against certain biofilms potentially harmful in the food industry.

ADERSE EVENTS:

A review of MHRA and BFarm websites 2016-2020 revealed no adverse event with enzymatic cleaners.

CONCLUSION ON LITERATURE REVIEW.

Whilst a thorough review of the state of the art concerning enzymatic cleaners was not required, it is interesting to note that the 3 articles referenced above 6.1.1 to 6.1.3 found in Pubmed confirmed the efficacy of enzymatic cleaners in removing biofilms.

No adverse events were identified with Viruzyme or competitive products in the period reviewed (2016-2020).

7. COMPLIANCE WITH ANNEX X - CLINICAL EVALUATION

1. General provisions

1.1. As a general rule, confirmation of conformity with the requirements concerning the characteristics and performances referred to in Sections 1 and 3 of Annex I, under the normal conditions of use of the device, and the evaluation of the side-effects and of the acceptability of the benefit/risk ratio referred to in Section 6 of Annex I, must be based on clinical data. The evaluation of this data, hereinafter referred to as 'clinical evaluation', where appropriate taking account of any relevant harmonised standards, must follow a defined and methodologically sound procedure based on:

Risk Management:

Risk Management Report: AMI-TD-VZF-RMR-01
Hazard Identification Report: AMI-TD-SGF-RHR-01
Risk Management Report: AMI-TD-VZF-RMR-01

Compliance with relevant Standards:

Relevant harmonised Standards: AMITY/TD-VZF-5.2

1.1.1. Either a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, where:

Intended purpose: see AMI-TD-VZF-1.1 AND -1.3 i.e. cleaning of surgical instruments

The cleaning process has been validated: See document TD-VZ 2.4

There are no contact with patient or user (if using gloves- IFU and data sheets specifies precautions).

— there is demonstration of equivalence of the device to the device to which the data relates, and

For a comparison of Viruzyme family to equivalent devices see section 5 above. Although equivalence is not fully claimed it is clear that there are a number of other similar devices on the market with similar claims and formulations to Viruzyme, many of which are CE marked.

— the data adequately demonstrate compliance with the relevant essential requirements.

See document Essential Requirements Checklist AMITY/TD-VZ 5.1

See section 6 above.

1.1.2. Or a critical evaluation of the results of all clinical investigations made.

N/A

1.1.3. Or a critical evaluation of the combined clinical data provided in 1.1.1 and 1.1.2.

See above.

1.1a In the case of implantable devices and devices in Class III clinical investigations shall be performed unless it is duly justified to rely on existing clinical data.

N/A

1.1b The clinical evaluation and its outcome shall be documented. This documentation shall be included and/or fully referenced in the technical documentation of the device.

See this document:

1.1c The clinical evaluation and its documentation must be actively updated with data obtained from the post-market surveillance. Where post-market clinical follow-up as part of the post-market surveillance plan for the device is not deemed necessary, this must be duly justified and documented.
It is proposed that only Post Market Surveillance is necessary not Post Market Clinical Follow up as this is a low risk device with no patient contact and no clinical significance. The latest Post Market Surveillance Report can be seen on document AMITY/TD-VZF-PMSR-01-20 which concluded there were no adverse events, incidents or customer complaints in the period 20.4.18 – 30.4.20 during which time over 140,000 litres were sold.

1.1d Where demonstration of conformity with essential requirements based on clinical data is not deemed appropriate, adequate justification for any such exclusion has to be given based on risk management output and under consideration of the specifics of the device/body interaction, the clinical performances intended and the claims of the manufacturer.

Only limited clinical data is necessary – see Summary points 1-5 above.

Adequacy of demonstration of conformity with the essential requirements by performance evaluation, bench testing and pre-clinical evaluation alone has to be duly substantiated.

Performance has been validated – see document TD-VZ 2.4

1.2. All the data must remain confidential, in accordance with the provisions of Article 20.

2. Clinical investigations

Not applicable. (N/A)

2.1. Objectives
The objectives of clinical investigation are:
— to verify that, under normal conditions of use, the performance of the devices conform to those referred to in Section 3 of Annex I, and
— to determine any undesirable side-effects, under normal conditions of use, and assess whether they constitute risks when weighed against the intended performance of the device.

2.2. Ethical considerations
►M5 Clinical investigations must be carried out in accordance with the Helsinki Declaration adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the World Medical Assembly. ◄ It is mandatory that all measures relating to the protection
▼B
of human subjects are carried out in the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results.

N/A

2.3. Methods
2.3.1. Clinical investigations must be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the manufacturer's claims for the device; these investigations must include an adequate number of observations to guarantee the scientific validity of the conclusions.
2.3.2. The procedures used to perform the investigations must be appropriate to the device under examination.
2.3.3. Clinical investigations must be performed in circumstances similar to the normal conditions of use of the device.

2.3.4. All the appropriate features, including those involving the safety and performances of the device, and its effect on patients must be examined.
▼M5

2.3.5. All serious adverse events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed.
▼B

2.3.6. The investigations must be performed under the responsibility of a medical practitioner or another authorized qualified person in an appropriate environment.
The medical practitioner or other authorized person must have access to the technical and clinical data regarding the device.

2.3.7. The written report, signed by the medical practitioner or other authorized person responsible, must contain a critical evaluation of all the data collected during the clinical investigation.

8. CONCLUSION

It is considered that this Clinical Evaluation confirms that the Amity Viruzyme range of products complies with ANNEX 1 Essential Requirements of MDD/93/42/EEC by consideration of:

1. Satisfactory risk assessment.
2. Process validation.
3. A cursory comparison with equivalent products for technical and safety but not clinical (there is no clinical application to the patient).
4. A cursory consideration of the literature for adverse events will be carried to confirm the absence of any adverse events with competitive products.
5. Compliance with the relevant harmonised Standards which are listed in the document referred to at AMITY/TD-VZF-5.2

We therefore conclude that the objectives of this clinical evaluation, which is to confirm the Viruzyme range of products comply with the Essential Requirements (MDD/93/42/EEC ANNEX I) by satisfactory compliance with the steps 1-5 listed above, have been met and that the Viruzyme range of products comply with their claims and are safe and can continue to be marketed as self-certified Class I devices according to MDD/93/42/EEC.

Checking this Clinical Evaluation for conformity with MEDDEV 2.1.7 rev 4 has not been considered appropriate as this is not a legal obligation and the Viruzyme Family of devices are low risk and have been confirmed as complying with the requirements of MDD/93/42/EEC ANNEX I by completion of the objectives 1-5 as set out in the Summary.