BIOCOMPATIBILITY SUMMARY

Tristel ORL is a high-level disinfectant foam intended to disinfect cleaned, reusable non-lumened otorhinolaryngology devices.

To gain marketing authorisation, Tristel has submitted a data set adhering to the requirements laid out in the following guidance:

- Health Canada guidance for 'Safety and Effectiveness Requirements for High-Level Disinfectants and Sterilants for use on Reusable Semi-Critical and Critical Medical Devices' (2018).
- Guidance for Industry and Food and Drug Administration Staff – Use of International Standard ISO 10993-1, Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing within a Risk Management Process, issued September 8, 2023.

Biocompatibility overview

In-line with regulatory guidance, Tristel ORL was subjected to a range of biocompatibility assessments.

Healthcare professionals who reprocess medical devices may be exposed to a disinfectant solution. Therefore, biocompatibility testing is a critical cornerstone of assessing product safety.

Disinfectant residues that remain on the surface of the devices following reprocessing have the potential to pose a risk to patients and/or users. Therefore, it is important that the disinfectant and the potential residues that can remain following reprocessing are assessed.

Tristel has focused its biocompatibility testing program on the potential toxicity of Tristel ORL to the user (with Tristel ORL prepared above maximum concentration), the toxicity of Tristel ORL when used in combination with Tristel ORL Wipes, and the toxicity of potential Tristel ORL residues and therefore the risk to the patient. These have been assessed through a battery of biocompatibility studies, which are summarized in Table 1.

All tests were carried out by third-party accredited laboratories.

Chemical Analysis

In addition to biocompatibility testing, Tristel has conducted chemical analysis to determine whether Tristel ORL potentially degraded materials and/or caused the formation of potentially harmful residues on medical devices that could pose a risk to the patient.

Any Tristel ORL residues remaining on three medical devices following disinfection with Tristel ORL have been assessed to determine non-volatile, semi-volatile and volatile organic compounds, heavy metals and certain inorganics which may be present in the residue after disinfection. The medical devices chosen were a mix of different shapes and materials of construction.

The medical devices were disinfected with Tristel ORL, with the dose of Tristel ORL used being at twice the volume of foam detailed in the Instructions for Use. This simulates a worst-case scenario, demonstrating a 100% safety margin. The devices were extracted in both polar and non-polar solvents to ensure anything present would be extracted, along with control devices which were not disinfected. The devices were incubated at 50 ± 2 °C for 72 ± 2 hours.

A toxicological risk assessment of the results was performed considering the adult population with a body weight equal to 70 kg.

Based on the results of the performed testing and analysis, together with the toxicological assessment, even at a worst case of double volume dose of 8 aliquots, no residue post device disinfection represents a toxicological concern. Tristel ORL is safe for its intended use under labeled directions for use.

Inhalation

To provide clarity on the risk posed to the user through inhalation of chlorine dioxide, Tristel has carried out a study, which measures the user exposure to chlorine dioxide over an eight hour shift carrying out 40 procedures. The acceptance criteria were based on the tightest limits available in accordance with the U.S. Occupational Safety and Health Administration (OSHA) legal airborne permissible exposure limit (PEL) for chlorine dioxide of 0.1 ppm averaged over eight hours and California Division of Occupational Safety and Health PEL of averaged 0.3ppm over a 15 minute period.

Over the course of testing, simulating 40 disinfection procedures performed over an 8-hour period using Tristel ORL, the average 8-hour TWA readings of 0.007 ppm did not exceed the U.S. OSHA permissible exposure limit of 0.1 ppm for chlorine dioxide, and the results of the average 15-minute STEL readings, 0.16 ppm, did not exceed the California Division of Occupational Safety and Health PEL of 0.3 ppm.

BIOCOMPATIBILITY SUMMARY

TABLE 1 – SUMMARY OF TRISTEL ORL'S BICOMPATIBILITY ENDPOINTS

BIOLOGICAL END-POINT	TEST ARTICLE	RESULTS
Acute Dermal Irritation	Base	**Slightly Irritating**
Acute Eye Irritation	Base	**Mildly Irritating**
Acute Inhalation	Base	**LC_{50} > 5.24 mg/L**
Acute Oral toxicity	Base	**LD_{50} > 5000 mg/kg**
Skin Sensitization	Base	**Not a sensitizer**
Acute Dermal Irritation	Activator	**Non Irritating**
Acute Eye Irritation	Activator	**Minimally Irritating**
Acute Inhalation	Activator	**LC_{50} > 5.61 mg/L**
Acute Oral toxicity	Activator	**LD_{50} > 5000 mg/kg**
Skin Sensitization	Activator	**Not a sensitizer**
Genotoxicity	Activated/in-use >max conc.	**Non-mutagenic & Non-clastogenic**
Skin Irritation	Activated/in-use >max conc.	**Slight Irritant**
Primary Eye Irritation	Activated/in-use >max conc.	**Eye irritant**
Skin Sensitization	Activated/in-use >max conc.	**Not a skin sensitizer**
Acute Oral toxicity	Activated/in-use >max conc.	**LD_{50} that is greater than 2000 mg/kg**
Cytotoxicity	WITH WIPE Activated/in-use >max conc.	**Not considered to have a cytotoxic effect**
Acute Dermal Irritation	WITH WIPE Activated/in-use >max conc.	**Negligible**
Skin Sensitization	WITH WIPE Activated/in-use >max conc.	**No sensitization potential**
Vaginal Irritation	RESIDUE after using WITH WIPE and MATERIALS OF CONSTRUCTION 2 x Activated/in-use >max conc.	**Non-irritating**
Rectal Irritation	RESIDUE after using WITH WIPE and MATERIALS OF CONSTRUCTION 2 x Activated/in-use >max conc.	**Non-irritating**
Skin irritation	RESIDUE after using WITH WIPE and MATERIALS OF CONSTRUCTION 2 x Activated/in-use >max conc.	**Non-irritating**
Cytotoxicity	RESIDUE after using WITH WIPE and DEVICE 2 x Activated/in-use >max conc.	**Not cytotoxic**

Conclusion

Tristel Precursors (Base/Activator) are:

- Assigned a Toxicity Category IV, rated minimally irritating with no positive effects exhibited in any eyes after treatment for acute eye irritation.
- Acute oral LD_{50} >5000mg/kg
- Assigned a Toxicity Category IV, rated as slightly irritating for primary dermal irritation study.
- Acute inhalation LC_{50} >5.24m/L (Base) >5.61m/L (Activator), with no clinical signs of toxicity during the study.
- Not considered a sensitizer, <3 stimulation index in all groups of Test animals.

Tristel ORL is:
Non-mutagenic according to the criterion of OECD 490 and OECD 471. Non-clastogenic to maturing erythrocytes according to the criterion of OECD 474, and slightly irritating to the dermis according to the test criterion of OECD 404. It has a LD50>2000mg/kg. It is an eye irritant in accordance with OECD 405 and not considered to be a skin sensitizer according to (ISO 10993-10).

Tristel ORL with Tristel ORL Wipes is:
Not considered to have a cytotoxic effect according to the criterion of ISO 10993-5 and according to criterion of ISO 10993-10, does not cause sensitization and is a negligible irritant.

Tristel ORL Foam at residue levels is:
Not considered irritating to vaginal mucosa or rectal tissue when extracted in saline or cottonseed oil. In dermal irritation testing, the irritation response is classified as negligible in accordance with ISO 10993-23.

Does not degrade materials and/or cause the formation of potentially harmful residues on medical devices that could pose a risk to the patient. Based on the results of performed testing and analysis, together with the toxicological assessment even at a worst case of double volume dose of 8 aliquots, no residue post device disinfection represents a toxicological concern.

History of clinical use or human exposure data

Chlorine dioxide as an aqueous solution is classified, at high concentrations of >0.3%, according to the European Regulation (EC) No 1272/2008 on classification, labeling and packaging of substances and mixtures (CLP). The CLP Regulation adopts the United Nations' Globally Harmonised System. The percentage of chlorine dioxide in activated Tristel ORL is 0.03-0.14% and below the percentage band 0.3% which classifies it as hazardous. CLP classification of chlorine dioxide generated in Tristel ORL is non-hazardous.

Tristel ORL products are marketed in Europe since, and Tristel estimates that Tristel ORL has been used in over half a million disinfection procedures in ENT. During this period of active sale and use, no adverse events associated with the use of Tristel ORL products have been reported to Tristel through the European, or any other, Vigilance Systems.

In conclusion, test results show that there is a very low potential for any unacceptable adverse biological response resulting from contact of the component materials of the device with the body of a patient. Although testing shows that Tristel ORL can be slightly irritating to the dermis of the user, and is an eye irritant, the risk is mitigated through device labeling instructing the user to wear gloves and safety glasses.