File No.: LTD/2128

February 2021

AUSTRALIAN INDUSTRIAL CHEMICALS INTRODUCTION SCHEME (AICIS)

PUBLIC REPORT

2-Butenedioic acid (2*Z*)-, polymer with 2-methoxyethene, calcium zinc salt (INCI Name: Calcium/Zinc PVM/MA Copolymer)

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals Act 2019 (the IC Act) and Industrial Chemicals (General) Rules 2019 (the IC Rules) by following the Industrial Chemicals (Consequential Amendments and Transitional Provisions) Act 2019 (the Transitional Act) and Industrial Chemicals (Consequential Amendments and Transitional Provisions) Rules 2019 (the Transitional Rules)*. The legislations are Acts of the Commonwealth of Australia. The Australian Industrial Chemicals Introduction Scheme (AICIS) is administered by the Department of Health, and conducts the risk assessment for human health. The assessment of environmental risk is conducted by the Department of Agriculture, Water and the Environment.

This Public Report is available for viewing and downloading from the AICIS website. For enquiries please contact AICIS at:

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Executive Director
AICIS

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SUMMARY

The following details will be published on the AICIS website:

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/2128	Procter & Gamble Australia Pty Ltd	2-Butenedioic acid (2*Z*)-, polymer with 2-methoxyethene, calcium zinc salt (INCI Name: Calcium/Zinc PVM/MA Copolymer)	ND*	≤ 15 tonnes per annum	Component of denture adhesive

*ND = Not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard Classification
As no toxicity data were provided, the assessed polymer cannot be classified according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia.

Human Health Risk Assessment
Under the conditions of the occupational settings described, the assessed polymer is not considered to pose an unreasonable risk to the health of workers.

Provided that clear use instructions to consumers are included in labels or leaflets of products containing the assessed polymer, the assessed polymer is not considered to pose an unreasonable risk to public health.

Environmental Risk Assessment
Based on the assumed low environmental hazard of the polymer and the Australian water quality guidelines for zinc, the assessed polymer including its counterions are not considered to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES

Public Health

- Products containing the assessed polymer available to the public should include the following:
  - To follow instructions provided with the denture adhesive product.
  - The product contains zinc as an ingredient.
  - Not to use more adhesive than recommended.
  - Use directions that will prevent overuse such as graphics of the amount of adhesive to use or the amount of time that a tube should last under correct usage.

Emergency procedures

- Spills or accidental release of the assessed polymer should be handled by physical containment, collection and subsequent safe disposal.

Disposal

- Where reuse or recycling are not appropriate, dispose of the assessed polymer in an environmentally sound manner in accordance with relevant Commonwealth, state, territory and local government legislation.

Regulatory Obligations

Specific Requirements to Provide Information
This risk assessment is based on the information available at the time of the application. The Executive Director may initiate an evaluation of the chemical based on changes in certain circumstances. Under Section 101 of the IC Act the applicant of the assessed chemical has post-assessment regulatory obligations to provide information to AICIS when any of these circumstances change. These obligations apply even when the assessed polymer is listed on the Australian Inventory of Industrial Chemicals (the Inventory).

Therefore, the Executive Director of AICIS must be advised in writing within 20 working days by the applicant or other introducers if:

- the use concentration of the assessed polymer exceeds 40% in denture adhesive products;
- the polymer has a number-average molecular weight of less than 1,000 g/mol;
- the function or use of the polymer has changed from a component of denture adhesive, or is likely to change significantly;
- the amount of polymer being introduced has increased, or is likely to increase, significantly;
- the polymer has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the polymer on human health, or the environment.

The Executive Director will then decide whether an evaluation of the introduction is required.

Safety Data Sheet
The SDS of a product containing the assessed polymer provided by the applicant was reviewed by AICIS. The accuracy of the information on the SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND APPLICATION DETAILS

APPLICANT(S)
Procter & Gamble Australia Pty Ltd (ABN: 91 008 396 245)
Level 4, Innovation Road
MACQUARIE PARK NSW 2113

APPLICATION CATEGORY
Limited: Synthetic polymer with number average molecular weight (Mn) ≥ 1,000 g/mol

PROTECTED INFORMATION (SECTION 38 OF THE TRANSITIONAL ACT)
Data items and details exempt from publication include: structural formula, molecular weight, analytical data, degree of purity, polymer constituents, residual monomers, impurities, additives/adjuvants, use details, import volume and identity of manufacturer.

VARIATION OF DATA REQUIREMENTS (SECTION 6 OF THE TRANSITIONAL RULES)
Schedule data requirements are varied for all physical and chemical properties except for density and particle size.

PREVIOUS APPLICATION IN AUSTRALIA BY APPLICANT(S)
None

APPLICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

CHEMICAL NAME
2-Butenedioic acid (2*Z*)-, polymer with 2-methoxyethene, calcium zinc salt

OTHER NAME(S)
Calcium/Zinc PVM/MA Copolymer (INCI name)

CAS NUMBER
133222-51-2

MOLECULAR FORMULA
$(C_4H_4O_4.C_3H_6O)_x$xCa.xZn

MOLECULAR WEIGHT
Number average molecular weight (Mn) is > 10,000 g/mol.

ANALYTICAL DATA
Reference IR and GPC spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 80 %

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: solid white powder

Property	*Value*	*Data Source/Justification*
Melting Point/Freezing Point	154 °C	Glass transition temperature for the starting monomer
Boiling Point	Not determined	Imported in formulation

Property	*Value*	*Data Source/Justification*
Density	479 kg/m^3 (bulk density) 720 kg/m^3 (tapped density, 4,000 taps)	Measured
Vapour Pressure	Not determined	Imported in formulation
Water Solubility	Not determined	Water dispersible polymer
Hydrolysis as a Function of pH	Not determined	Does not contain hydrolysable functionalities
Partition Coefficient (n-octanol/water)	Not determined	Not relevant
Adsorption/Desorption	Not determined	Both the anionic and cationic components of the assessed polymer have potential to partition or sorb to soil
Dissociation Constant	Not determined	Contains ionisable functionalities with an expected pKa of approximately 4.
Particle Size	Inhalable fraction (< 100 μm): 100% Respirable fraction (< 10 μm): 41.3% VWAD* = 13 μm	Measured
Flash Point	Not determined	Imported in formulation
Autoignition Temperature	Not determined	Imported in formulation
Explosive Properties	200-250 g/m^3 (Minimum Explosible Concentration)	Measured
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidative properties

*VWMD = Volume weighted mean diameter

DISCUSSION OF PROPERTIES
For details of tests on physical and chemical properties, refer to Appendix A.

Reactivity
The assessed polymer is expected to be stable under normal conditions of use.

Physical Hazard Classification
Based on the submitted physico-chemical data depicted in the above table, the assessed polymer is not recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF ASSESSED CHEMICAL (100%) OVER NEXT 5 YEARS
The assessed polymer will not be manufactured or reformulated in Australia. It will be imported in end-use products at ≤ 40% concentration.

MAXIMUM INTRODUCTION VOLUME OF ASSESSED CHEMICAL (100%) OVER NEXT 5 YEARS

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	≤ 10	≤ 10	≤ 10	≤ 15	≤ 15

PORT OF ENTRY
Sydney

IDENTITY OF RECIPIENTS
Procter & Gamble Australia Pty Ltd

TRANSPORTATION AND PACKAGING
The assessed polymer will be imported into Australia as a component of formulated denture adhesive products in tubes/containers suitable for retail sale and then transported by road for distribution to commercial warehouses and retail stores within Australia.

USE
The assessed polymer will be used as a component of denture adhesive at ≤ 40% concentration.

The assessed polymer at ≤ 40% concentration will not be manufactured or reformulated in Australia. It will be imported into Australia as a component of denture adhesive products for use by the general public.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport, warehouse and retail workers	up to 8	up to 260

EXPOSURE DETAILS
Transport, warehouse and retail workers may be exposed to the assessed polymer (at ≤ 40% concentration) only in the event of accidental rupture of packages.

6.1.2. Public Exposure
There will be repeated exposure of the public to the assessed polymer at ≤ 40% concentration in denture adhesive products. The principal route of exposure will be oral, while accidental dermal and ocular exposure is also possible.

6.2. Human Health Effects Assessment
No toxicity data were provided on the assessed polymer. However, the assessed polymer is not expected to be absorbed across biological membranes based on its very high molecular weight (> 10,000 g/mol) and very low percentage (< 1%) of low molecular weight species < 1,000 g/mol.

Zinc is an essential element playing an important role in many processes in the body. However excess exposure to humans over natural background levels can lead to adverse effects mainly related to its ability to induce copper deficiency.

An excess of zinc in the body can lead to health problems such as nerve damage, especially in the hands and feet. This damage appears slowly, over an extended period of time.

The upper limits (UL) of oral zinc intake established by various agencies across the globe were included in the below table.

Organisation	**Established Zinc Upper Level**
World Health Organization (WHO) (2004)	UL of 45 mg/day (adult male) (equal to 0.64 mg/kg/day in a 7 0kg adult)
Agency for Toxic Substances and Disease Registry (ATSDR) (2005)	Minimal Risk Level of 0.3 mg/kg/day (equal to 18 mg/day for a 60 kg adult)
US Environmental Protection Agency (EPA) (2005)	Reference Dose for Chronic Oral Exposure of 0.3 mg/kg/day (equal to 18 mg/day for a 60 kg adult)
Council for Responsible Nutrition (CRN) (2014)	UL (Supplemental) of 30 mg/day
Expert Group on Vitamins and Minerals (EVM) (UK) (2003)	UL (Supplemental) of 25 mg/day
Scientific Committee on Food (SCF) (EU) (2003)	Tolerable Upper Intake Level of 25 mg/day
Institute of Medicine (2001) US	Tolerable Upper Intake Level of 40 mg/day
Joint FAO/WHO Expert Committee on Food Additives (2006)	Maximum tolerable daily intake of 0.3 - 1 mg/kg (equal to 18 - 60 mg/day for a 60 kg adult)

Health Hazard Classification
As no toxicity data were provided, the assessed polymer cannot be classified according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia.

6.3. Human Health Risk Characterisation
The assessed polymer is expected to be of low systemic toxicity due to low absorption through oral mucosa based on the very high molecular weight and very low percentage of low molecular weight species.

6.3.1. Occupational Health and Safety
Transport, warehouse and retail workers may be exposed to the assessed polymer (at ≤ 40% concentration) only if the packages are ruptured. No other worker exposure is expected to the assessed polymer.

Under the conditions of the occupational settings described, the assessed polymer is not considered to pose an unreasonable risk to the health of workers.

6.3.2. Public Health
Members of the public may experience repeated exposure to the assessed polymer through the use of denture adhesive containing the assessed polymer at ≤ 40% concentration. The main route of exposure is expected to be oral, with some potential for dermal or accidental ocular exposure. Although data for the assessed polymer are not available, significant systemic exposure is not expected from use of the assessed polymer in denture adhesive products given the high molecular weight and very low percentage of low molecular weight species < 1,000 g/mol in the assessed polymer limiting dermal absorption.

Estimate of daily Zn exposure from use of denture adhesive products containing the assessed polymer (worst case scenario):

Average daily use of the denture adhesive product	1.5 g (P&G CL2010068)
Level of assessed polymer in the product	≤ 40%
Level of zinc in the polymer	< 6%
Systemic availability of Zinc*	≤ 12.6% (P&G CL2009110 and CL2010123)

*Based on very high molecular weight (> 10,000 g/mol) and very low percentage of low molecular weight species < 1,000 g/mol of the assessed polymer, systemic availability of Zinc from denture adhesive products after application by users is expected to be much lower than 12.6%, which is the worst case scenario. Leaching of zinc from the polymer is not expected under normal use conditions.

The maximum worst case zinc exposure level from using denture adhesive products = 1.5 g × 1,000 × 40% × 6% × 12.6% = 4.54 mg zinc per day

This value will be further reduced to 3.14 mg zinc/day if zinc ingestion is 69.3% of maximum daily use as indicated by the applicant (P&G CL2010065).

As the upper limits of oral zinc intake established by various agencies across the globe are 18-60 mg/day (see section 6.2) and the average recommended amounts for adult intake of zinc is reported to be at 11 mg/day for man and 8 mg/day for women (NIH 2020), the maximum zinc exposure level calculated above from using denture adhesive products containing the assessed polymer at ≤ 40% concentration is not considered to pose an unreasonable risk to public health.

Overuse of zinc-containing denture adhesives, especially when combined with dietary supplements containing zinc and other sources of zinc, can contribute to an excess of zinc in human body (FDA 2018).

The FDA was aware of case reports in the medical literature linking negative reactions such as nerve damage, numbness or tingling sensations in users of denture adhesives that contain zinc with chronic overuse of those products. The FDA also received reports of adverse events linked to use of denture adhesives. While some product instructions indicated that one tube should last seven to eight weeks, the subjects of the negative case reports had used at least two tubes of zinc-containing denture adhesive each week. The FDA had not found conclusive evidence that these problems resulted from using zinc-containing denture adhesive as instructed in the product labelling (FDA, 2018).

To help address any potential risks to public from overuse of zinc-containing denture adhesives, introducers of zinc-containing denture adhesives into Australia should consider:

- Including safety directions on denture adhesive product labels to prevent overuse of products containing zinc.
- Product labels should indicate that zinc is present as an ingredient in the adhesive product.

Provided that clear instructions to consumers as indicated above are included in labels or leaflets of products containing the assessed polymer, the assessed polymer is not considered to pose an unreasonable risk to public health.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The assessed polymer will not be manufactured or reformulated in Australia. The assessed polymer will only be imported as a component of finished denture adhesive products. There is unlikely to be any significant release to the environment from transport and storage, except in the case of accidental rupture of packages. In the event of spills, the product containing the assessed polymer is expected to be collected with inert material and disposed of to landfill in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE
The assessed polymer will be primarily washed into the sewers during use of denture adhesive product.

RELEASE OF CHEMICAL FROM DISPOSAL
Wastes and residues of the assessed polymer in empty end-use containers (1-2% of the total volume estimated by the applicant) are likely to either share the fate of the container and be disposed of to landfill, or be released to sewer when packaging is rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in denture adhesives, the majority of the assessed polymer will enter the sewers and be treated at sewage treatment plants (STPs) before the potential release to surface waters nationwide.

The assessed polymer is a mixed salt and expected to ionise and exchange ions with potential release of cationic metals in the STPs. The anionic component of the assessed polymer is expected to be partially removed via partitioning to the sludge based on removal rates of high molecular weight anionic polymers in wastewater treatment tests (Boethling and Nabholz, 1997). The distribution of released metals (zinc) between solution and solid phases is related to the pH, nature and concentration of complexing agents, sludge age, treatment methods and other factors. Reported zinc removal rates by activated sludge, trickling filter and membrane bioreactor sludge are in the range between 30 and 99% (Santos et al., 2010).

A proportion of the assessed polymer may be applied to land when effluent is used for irrigation or when sewage sludge is used for soil remediation, or disposed of to landfill. In surface water, soils or landfill, the anionic component of the assessed polymer is not expected to bioaccumulate based on its high molecular weight and will slowly degrade through biotic and abiotic processes to form water and oxides of carbon.

The cationic component, zinc, is an essential element needed by organisms. Aquatic organisms are known to bioconcentrate zinc from water. The concentration at which zinc is homoeostatically regulated is species-specific and the external zinc concentration at which regulation breaks down depends on both intrinsic (e.g., species) and extrinsic (e.g., temperature, pH and presence of other metals) factors. Accumulation of zinc to meet physiological requirements can be mistaken for trophic transfer, however, zinc is not biomagnified (WHO, 2001).

7.1.3. Predicted Environmental Concentration (PEC)

Aquatic compartment
The predicted environmental concentration (PEC) has been calculated to assume a worst-case scenario, with 100% release of the assessed polymer into sewer systems nationwide and no removal within sewage treatment plants (STPs).

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	15,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	15,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	41.10	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	24.386	million
Removal within STP	0%	
Daily effluent production:	4,877	ML
Dilution Factor – River	1.0	
Dilution Factor – Ocean	10.0	
PEC - River:	8.43	µg/L
PEC - Ocean:	0.84	µg/L

The worst-case release of the assessed polymer is 8.43 and 0.84 µg/L in river and marine water (see above), corresponding to < 0.51 and < 0.05 µg/L zinc in river and marine water based on Zn being < 6% of the weight of the starting material.

Soil compartment
The assessed polymer may be also released into soils as a result of application of biosolids to agricultural soils. The predicted environmental concentration (PEC) in biosolids has been calculated to assume a worst-case scenario, with 100% removal rate of cationic and anionic components of the assessed polymer within sewage treatment plants (STPs). Under this scenario, partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 84,261 µg/kg (dry wt.) of assessed polymer corresponding to 5,056 µg/kg zinc which is a function of the quantity of effluent and dry weight volume of biosolids production, 100 kg/ML effluent. Biosolids are applied to agricultural soils, with an assumed average rate of 10 t/ha/year. Assuming a soil bulk density of 1,500 kg/m^3 and a soil-mixing zone of 10 cm, the concentration of the assessed polymer may approximate 562 µg/kg of assessed polymer (< 33.7 µg/kg of zinc) in applied soil. Assuming accumulation of the assessed polymer in soil for 5 and 10 years under repeated biosolids application, the concentration of assessed polymer in the applied soil in 5 and 10 years may approximate 2,809 µg/kg polymer (< 169 µg/kg zinc) and 5,617 µg/kg (< 337 µg/kg zinc), respectively.

Re-use of STP effluent for irrigation purposes will result in significantly lower concentration in biosolids than direct application of biosolids to agricultural soils.

7.2. Environmental Effects Assessment
The anionic component of the assessed polymer is expected to show low toxicity across three trophic levels. Anionic polymers are generally of low toxicity to fish and daphnia, however they are known to be moderately toxic to algae. The mode of toxic action is over-chelation of nutrient elements needed by algae for growth. The highest toxicity is when the acid is on alternating carbons of the polymer backbone, leading to chelation of essential nutrients (Boethling and Nabholz, 1997). This is not the case with the assessed polymer, which should have a lower toxicity. In addition, when enough calcium is added to a polymer to satisfy its anionic charges, algal toxicity is observed to be mitigated.

A small proportion of released zinc may be bioavailable to aquatic organisms and the toxicity of the assessed polymer may be attributed to the cationic component (zinc). Generally, zinc bioavailability and toxicity is affected by biotic and abiotic factors including organism age and size, water hardness, pH, cationic exchange capacity, dissolved organic carbon and temperature (WHO, 2001). Zinc in ionic form may be very toxic to aquatic life. However, zinc ionic forms are not expected to be present in significant amounts, in the natural environment, therefore, the ANZECC/ARMCANZ (2000) guideline limits for zinc in surface waters for ecosystem protection will be considered as more representative for risk characterisation purposes.

Therefore, the assessed polymer is not formally classified under the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)* (United Nations, 2009) for acute and chronic toxicity. The assessed polymer is expected to release metals which may transform to other chemical compounds under the environmental conditions.

7.2.1. Predicted No-Effect Concentration

The predicted No-Effect Concentrations has not been calculated for the anionic component of the assessed polymer due to expected low toxicity.

For the zinc counterion, the ANZECC/ARMCANZ (2000) Water Quality Guideline (WQG) limit for zinc in surface waters for ecosystem protection is 8 µg/L in freshwater (at a hardness of 30 mg $CaCO_3$/L) and 15 µg/L in marine environment.

7.3. Environmental Risk Assessment

The anionic component of the assessed polymer is not expected to reach ecotoxicologically significant concentrations in the aquatic and soil environment. The anionic component of the assessed polymer has a low potential for bioaccumulation and is likely to biodegrade slowly in surface waters or soils.

The contribution of the assessed polymer as an anthropogenic source of zinc, at the proposed import volume and use pattern, has been compared to Australian water quality guideline limits. At the proposed use patterns the assessed polymer may lead to the maximum predicted environmental concentrations in surface waters of 0.51 µg/L zinc which is significantly lower than WQG guideline limit for zinc in surface waters. Background zinc concentrations in Australian surface waters have been reported as 0.9 µg/L in fresh water (ANZECC/ARMCANZ, 2000). The release of zinc from the use of the assessed polymer in Australia is not expected to significantly increase the background concentration of this element in environmental waters.

Background zinc concentrations in Australian soils range 1-263 mg/kg, with a calculated median background zinc concentration in soil of 39 mg/kg (Berkman, 1989). At the proposed use pattern, assuming 100% removal rate of zinc by sludge, may lead to < 0.34 mg/kg increase in zinc concentrations in agricultural soils over a 10 year period due to the application of biosolids. This represents a 0.87% increase with respect to the median background concentration. Therefore, the contribution of the assessed polymer as an anthropogenic source of zinc is not expected to result in a significant increase to the concentration of zinc in soils with respect to background values. Similarly, the concentration of zinc in sediment will be dependent on its fate and behaviour in the whole aquatic system including the overlying water and no significant increase in environmental levels of zinc, in sediment is expected.

Therefore, the assessed polymer including its counterions are not considered to pose an unreasonable risk to the environment, based on the assumed low environmental hazard of the polymer and the Australian water quality guidelines for zinc.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Density 479 kg/m^3 (bulk density)
720 kg/m^3 (tapped density, 4,000 taps)

Method In house method.
Remarks Density is calculated as mass/volume and obtained by adding a known mass of chemical powder to a graduated cylinder. Tapped density is obtained by tapping a graduated cylinder containing the powder sample until little further volume change is observed.
Test Facility P & G (done on 22 April 2020)

Particle Size

Method In house method.

Range (µm)	*Mass (%)*
< 100	100
< 10	41.3

Volume weighted mean diameter = 13.013 µm

Remarks Laser light scattering on Malvern 2000 particle sizer was used.
Test Facility P & G (2019)

Explosive Properties 200-250 g/m^3 (Minimum Explosible Concentration)

Method In house method
Remarks Determination of explosive properties by using the Dust Explosibility Classification Test. The material was further evaluated in terms of Ignition Sensitivity included Minimum Ignition Temperature (MIT) determinations.
Test Facility Dekra Insight (2017)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Plasma Zinc Following Oral Application of Denture Adhesive

TEST SUBSTANCE: Fixodent denture adhesive cream (containing 16.67 mg zinc/g cream)

METHOD

Remarks – Method: Eleven out of 13 healthy male adult subjects completed the study after receiving a single oral dose of 3 g or 6 g of Fixodent denture adhesive cream containing approximately 50 mg and 100 mg of zinc, respectively. Subjects received Galzin (zinc acetate containing 50 mg zinc) as a positive control. In addition to plasma zinc, plasma copper and serum ceruloplasmin were analysed. Pharmacokinetic parameters for plasma zinc included area under the plasma concentration versus time curve (AUC_{0-24}), maximum plasma concentration (C_{max}) and time at which maximum plasma concentration was noted (t_{max}). Plasma zinc was analysed using both baseline uncorrected and baseline corrected data. Baseline uncorrected data were plasma measurements including both the endogenous levels of plasma zinc and exogenous contributions to plasma zinc. Baseline corrected data accounted and corrected for endogenous levels of plasma zinc, to allow for the accurate evaluation of changes in plasma zinc due to treatments.

RESULTS

Remarks – Results: There were no mortalities and no serious adverse events reported during the study. No changes were observed in test subjects for plasma copper or serum ceruloplasmin, compared to the baseline values.

The t_{max} for both denture adhesive cream and zinc acetate occurred at approximately 2 h.

Fifty mg zinc as denture adhesive cream showed a C_{max} that was 12% that of 50 mg zinc as zinc acetate. The dose of 100 mg zinc as denture adhesive cream showed a C_{max} that was 17.6% of 50 mg zinc as zinc acetate. The relative C_{max} would be 8.8% considering that 100 mg zinc as denture adhesive cream contained double the amount of zinc as the zinc acetate control.

Fifty mg of zinc as denture adhesive cream showed an AUC_{0-24} that was 12.6% of 50 mg zinc as zinc acetate. The dose of 100 mg zinc as denture adhesive cream showed an AUC_{0-24} that was 16.8% of 50 mg zinc as zinc acetate. The relative bioavailability would be 8.4% considering that 100 mg zinc as denture adhesive cream contained double the amount of zinc as the zinc acetate control.

The time of maximum zinc concentration (t_{max}) was similar between the Fixodent groups (3 g and 6 g) and zinc acetate, approximately 2 hours after application. The systemic exposures to zinc from Fixodent 6 g were not much greater than Fixodent 3 g even though the 6 g product had twice the amount of elemental zinc (100 mg versus 50 mg) relative to the 3 g product.

CONCLUSION: Lower systemic exposure to zinc from both doses of Fixodent product relative to Galzin after a single oral application was reported.

TEST FACILITY: CL 2009110 (2010)

B.2. Clinical Study to Assess Denture Fit and Adhesive Consumption Habits among Complete Denture Population

TEST SUBSTANCE: Fixodent denture adhesive

METHOD

Remarks – Method: Kapur method for scoring denture retention and stability was used among 375 subjects of adult denture adhesive users (at least 3 days per week). Only 300 subjects who met all inclusion/exclusion criteria and completed the study. Subjects were given denture adhesive product and written instructions for use at home for two weeks. The weight of the denture adhesive tube was recorded before and after use. Kapur score was from 0 to 3 where sum score is poor for < 3, fair for 3-4 and good for > 4. Results were measured for all subjects (314), including subjects with maxillary and mandibular dentures (167) and subjects with only maxillary dentures (143).

RESULTS

Remarks – Results: The mean (median) amount of denture adhesive used per day was 1.34 (1.12) g among all study participants (314), with 1.54 (1.33) g among those with both maxillary and mandibular dentures (167) and 1.14 (0.94) g among participants with maxillary dentures only (143).

The mean (median) number of adhesive applications per day was 1.33 (1.0) times among all study participants, with 1.44 (1.1) times among those with both maxillary and mandibular dentures and 1.20 (1.0) times among participants with maxillary dentures only.

The mean (median) amount of denture adhesive used per application was 1.10 (0.93) g among all study participants, with 1.18 (1.02) g among those with both maxillary and mandibular dentures and 1.02 (0.85) g among participants with maxillary dentures only.

CONCLUSION: The denture adhesive was found to be well tolerated.

TEST FACILITY: CS 2010068 (2010)

B.3. Study to Assess the In-Situ Retention of a Marketed Cream Denture Adhesive

TEST SUBSTANCE: Fixodent denture adhesive cream (containing Zn at 1.74%)

METHOD

Remarks – Method: Fifty adult denture wearers having complete maxillary and mandibular dentures were regular adhesive users (at least three times a week up to five days per week and up to 13 hours usage per day) for this study. Subjects used the product five times over the course of 5 days. At the completion of each product usage, the subjects' maxillary and mandibular dentures were removed and any retained denture adhesive was collected from both the dentures and the subjects' denture bearing area. The collected denture adhesive was weighed and analysed for zinc. Denture fit was determined using the Kapur scale method.

Weight of Adhesive Applied (mg) Summary			
Measure	Overall	Maxillary	Mandibular
Mean ± SD	917 ± 648	509 ± 380	404 ± 295
Min.-Max.	51 – 3,902	11- 2,420	40 – 1,747
Median	756	414	318

Percent of soluble zinc recovered was calculated from the dentures and the denture bearing surfaces, using the following formula: 100% × (zinc concentration of recovered sample × weight of adhesive recovered) divided by (zinc concentration of applied adhesive × weight of applied adhesive).

RESULTS

Remarks – Results: The dry weight of recovered denture adhesive was 543 mg, 426 mg, 366 mg, 305 mg and 267 mg at 1 h, 4 h, 7 h, 10 h, and 13 h post-denture insertion

respectively for maxillary and mandibular dentures combined. The percent of recovered denture adhesive out of applied dose was 62.0%, 46.8%, 37.8%, 28.8% and 25.9% at 1 h, 4 h, 7 h, 10 h, and 13 h post-denture insertion respectively for maxillary and mandibular dentures combined.

The percent of soluble zinc recovered from the denture adhesive was 64.7%, 53.3%, 44.3%, 33.7% and 30.7% at 1 h, 4 h, 7h, 10 h, and 13 h post-denture insertion respectively for maxillary and mandibular dentures combined.

CONCLUSION There were no adverse events reported during the study.

TEST FACILITY CL 2010065 (2011)

B.4. Systemic availability of Zinc from 6 grams of Fixodent Denture Adhesive

TEST SUBSTANCE Fixodent Free denture adhesive (containing 16.67 mg zinc/g cream)

METHOD

Remarks – Method Nineteen out of 20 healthy men and postmenopausal women subjects completed the study after receiving a single oral application of 6 g of Fixodent denture adhesive relative to a 25 mg zinc acetate capsule as Galzin. There were 2 application periods with one washout, 7 days apart. All subjects received a diet with a calculated value of less than 10 mg of zinc and less than 1 mg copper per day.

Subjects provided blood samples for Pharmacokinetics (PK) analysis of zinc plasma levels at the following time points in each dosing period:

Day -1: approximately 24 hours prior to dosing on day 1 (time 0 on day -1) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours following time 0;
Day 1: pre-dose (time 0 on Day 1) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 hours following dosing.
The following PK parameters for both baseline uncorrected and baseline corrected zinc were calculated using non-compartmental analysis in WinNonlin v5.1.1:
• Area under the plasma concentration versus time curve (AUC_{0-8});
• Maximum plasma concentration (C_{max});
• Time at which maximum plasma concentration being noted (t_{max});

Descriptive statistics were calculated for zinc concentrations (both baseline uncorrected and baseline corrected) by time and treatment. Maximum concentration (C_{max}) and time to maximum concentration (t_{max}) were obtained by direct observation. AUC_{0-8} was obtained by linear trapezoidal approximation of the concentration-time data. In addition, individual subject PK parameter ratios for C_{max} and AUC_{0-8} were calculated for each subject to evaluate exposures from the Fixodent treatment relative to the zinc acetate treatment.

RESULTS

Remarks – Results There were no mortalities, serious adverse events or withdrawals due to an adverse event during the period of the study. All events reported were assessed as mild in severity by the study authors.

There were no adverse events reported based on clinical laboratory or clinically significant changes in laboratory evaluations.

CONCLUSION The dose-adjusted relative systemic availability of zinc based on $AUC0_{-8}$ was 19.3% (baseline uncorrected) and 9.8% (baseline corrected) for Fixodent 6 g containing 100 mg elemental zinc relative to Galzin. The mean time to

	maximum concentration (t_{max}) for zinc was about 2-3 hours across both treatments for both baseline uncorrected and baseline corrected zinc. The results from the current study were consistent with the study 2009110 and showed low systemic availability for zinc from the Fixodent product relative to Galzin after single oral doses.
TEST FACILITY	CL 2010123 (2011)

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