ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nytox 1000 mg/g Powder for Solution for Fish Treatment in pouch [UK(NI)]
Cereka vet 1000 mg/g Powder for Solution for Fish Treatment in pouch [NO]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
1g of product contains 1g tricaine methanesulfonate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for Solution for Fish Treatment
White to off-white powder in a water soluble pouch.

4. CLINICAL PARTICULARS

4.1 Target species

1. Ornamental fish, or their development stages, and
2. Breeding and juvenile stages of fish.

4.2 Indications for use, specifying the target species

For use in an immersion bath for sedation, immobilisation and anaesthesia of fish for: vaccination, transportation, weighing, tagging, clipping, stripping of breed stock, blood-sampling and surgical procedures.

4.3 Contraindications

Do not use with the following tropical fish species:
Apistogramma (Mikrogeophagus) ramirez, Balantiocheilos melanopterus, Etroplus suratensis, Melanotaenia maccullochi, Monodactylus argenteus, Phenacogrammus interruptus and *Scatophagus argus.*

Do not use in cases of known hypersensitivity to the active substance.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

Do not exceed the dose recommended for each category of fish.
Brood stock anaesthetised for stripping should be immersed in unmedicated water immediately before collection of eggs or milt to avoid significant direct contact of either with the product.
As solutions of the veterinary medicinal product are slightly acidic, the use of phosphate or imidazole buffer has been proposed to reduce stress.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

People with known hypersensitivity to tricaine methanesulfonate should avoid contact with the veterinary medicinal product.

Impermeable rubber gloves should be worn when handling the veterinary medicinal product.

Avoid contact with skin and eyes. In case of accidental contact, immediately wash the affected area with plenty of clean running water. If irritation persists, seek medical advice.

Handle the pouches carefully to avoid breaking them. Do not create dust when handling the product. In case of accidental inhalation of dust, move to fresh air and if breathing is affected, seek medical advice immediately and show the package leaflet or the label to the physician.

In situations where dust is created when handling the product, wear a disposable half mask respirator conforming to European Standard EN 149 or a non-disposable respirator to European Standard EN 140 with a filter to EN 143.

Do not eat, drink or smoke whilst handling this product.

Wash hands after use.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Other Precautions:

In order to protect the environment, used solution either must be filtered using activated charcoal filters prior to dilution in the effluent to be discharged from the farm or it must be transferred to a holding tank filled with water with subsequent controlled release for dilution in the effluent to be discharged from the farm. See section 6.6.

4.6 Adverse reactions (frequency and seriousness)

None known.

4.7 Use during pregnancy, lactation or lay

Not applicable.

4.8 Interaction with other medicinal products and other forms of interaction

None known.

4.9 Amounts to be administered and administration route

An aqueous solution of the product is used in an immersion bath for sedation, immobilisation and anaesthesia of fish, both ornamental and those intended for human consumption.

A number of factors influence the efficacy and safety of the product, including concentration of the drug in water, duration of exposure, temperature, oxygen and density of biomass. Because of these variable factors it is strongly recommended that a test of the selected drug concentration and exposure time is conducted with a small group of representative fish before large numbers are medicated, particularly when water temperature is at the upper or lower ends of the normal temperature ranges for the species being treated. The product should be dissolved in water of the same composition and characteristics as that to which the fish are accustomed.

Calculate the total number of water-soluble pouches required for the intended dosage of the immersion bath. Place up to five of these pouches into a labelled screw-topped polyethylene container, together with a quantity of water (2 litres or more of water). Screw the lid tightly onto the container and gently shake for 5 minutes before adding to the immersion bath. Effects on the fish should be monitored as the product is gradually introduced.

Before anaesthesia, or prolonged sedation, fish should be fasted for 12 to 24 hours. During treatment they should be stocked at a density not exceeding 80g/litre. To minimise damage and loss when medicated for long periods for transport etc. the level of sedation should allow fish to maintain their equilibrium and swimming position. Aeration should be provided unless sedation, or anaesthesia, is of short duration. In anaesthesia loss of reflexes takes place in one to fifteen minutes after immersion depending upon concentration employed. Narcotised fish should be removed from medicated water and returned to their normal environment as soon as possible, when recovery will take between one and thirty minutes.

The following examples of dose rates and exposure times are based on laboratory and field experience:-

		Concentration Mg/litre of water	Immersion time (mins)
Trout species (7-17ºC)			
Sedation		10-30	Up to 480
Anaesthesia	Light	30-80	Up to 30
	Deeper	80-180	Up to 10
Salmon species			
Sedation		7-30	Up to 240
Anaesthesia	Light	30-80	Up to 10
	Deeper	80-100	Up to 5
Bass species			
Sedation		8-30	Up to 480
Anaesthesia	Light	30-70	Up to 20
	Deeper	70-100	Up to 4
Carp species			
Sedation		20-30	Up to 1440
Anaesthesia		30-200	Up to 8
Fresh water tropical fish			
Sedation		30-50	Up to 1440

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Remove fish immediately to aerated water of the same composition and temperature that is free from anaesthetic. Overdose or prolonged exposure to the product may cause respiratory failure and death.

4.11 Withdrawal period(s)

Withdrawal period: 70 degree days after the end of treatment.
Fish must not be slaughtered for human consumption during treatment.
Do not use during stripping of fish eggs intended for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Anaesthetics, anaesthetics general, other general anaesthetics
ATC vet code: QN01AX93

5.1 Pharmacodynamic properties

Tricaine methanesulfonate has properties slightly different from, but similar to, both ester and amide anaesthetics, acting as a general anaesthetic or narcotic. It is more water-soluble than benzocaine, lending it to fish application. The drug causes reduced blood flow through the gills and reduced oxygen consumption. The rate at which narcosis is induced depends upon the concentration of the product in water and also upon the water temperature. At higher temperatures onset or narcosis is more rapid; however the safety margin is less. Immersion of fish in unmedicated water reverses narcotic effects.

5.2 Pharmacokinetic particulars

Fish are normally immersed in solutions and both absorption and excretion occur through the gill epithelium. It is soluble in lipids, which probably accounts for its rapid diffusion across gills in both directions, with rapid anaesthesia and rapid recovery. Excretion occurs mainly across the gill epithelium. Non-polar ethyl meta-aminobenzoate and its N-acetyl derivative are both excreted across the gills, whereas the polar meta-aminobenzoic acid and its N-acetyl derivative are excreted via the kidneys. All species tested appear to produce an acetylated derivative, to the extent normally of less than 20% of the original anaesthetic. The hydrolysis to produce the free acid also varies with species, so the kidney excretion varies with species. However, the effectiveness varies less between species owing to the free movement of the drug across the gills.

The concentration in salmonid muscle, whilst the fish is under anaesthetic, ranges from 9.4 to 72.0 mg/kg. The half life of the anaesthetic in muscle on withdrawal is approximately 70 minutes. Thus 24 hours gives 20 half lives. The highest concentrations found in salmonid muscle after 24 hours have been 2.6 to 3.2 mg/kg (the oral LD in a 30kg dog is 30,000 x 4mg of the anaesthetic).

Environmental properties

None known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 30 months.
Shelf life after reconstitution according to directions: 12 hours.

6.4. Special precautions for storage

Store in a dry place.
Store in the original outer package.
Protect solution from direct sunlight.

6.5 Nature and composition of immediate packaging

Heat-sealed polyvinyl-alcohol water soluble pouch containing 10g or 50g of product contained in a sealed aluminium/polyethylene sachet.
20 sachets packed into a cardboard outer.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Used solution **must be transferred to a holding tank filled with water with subsequent controlled release** for dilution in the effluent to be discharged from the farm.

Transfer of used solution to a holding tank filled with water and controlled release for dilution in effluent will ensure that the concentration of spent tricaine methanesulfonate in discharge water does not exceed 1 $\mu g \cdot L^{-1}$. When releasing the solution from the holding tank, flow rates are calculated based on the following equation:

$$\text{Discharge (L/hr)} = \frac{\text{Farm flow rate (L/min)} \times 0.90 \text{ (safety factor)}}{\text{Holding tank concentration (mg/L)} \times 1000} \times 60$$

Eg. Holding tank concentration (mg/L)	Farm flow rate (L/min)	Discharge flow from holding tank (L/h)
10	10,000 / 20,000 / 30,000	54 / 110 / 160
50	10,000 / 20,000 / 30,000	11 / 22 / 32
100	10,000 / 20,000 / 30,000	5.4 / 11 / 16
200	10,000 / 20,000 / 30,000	2.7 / 5.4 / 8.1

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10 DATE OF REVISION OF THE TEXT

<[To be completed nationally]>

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER CARTON

(Outer carton contains 20 sachets)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nytox 1000 mg/g Powder for Solution for Fish Treatment in pouch [UK(NI)]
Cereka vet 1000 mg/g Powder for Solution for Fish Treatment in pouch[NO]

Tricaine methanesulfonate.

2. STATEMENT OF ACTIVE SUBSTANCES

1 g of product contains 1000 mg of tricaine methanesulfonate.

3. PHARMACEUTICAL FORM

Powder for Solution for Fish Treatment.

4. PACKAGE SIZE

20 x 10g
20 x 50g

5. TARGET SPECIES

Ornamental fish, or their development stages, and
Breeding and juvenile stages of fish.

6. INDICATION(S)

-

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Withdrawal period: 70 degree days after the end of treatment.
Fish must not be slaughtered for human consumption during treatment.
Do not use during stripping of fish eggs intended for human consumption.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once reconstituted use within 12 hours.

11. SPECIAL STORAGE CONDITIONS

Store in a dry place.
Store in the original outer package.
Protect solution from direct sunlight.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

16. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

10g or 50g Individual sealed aluminium/polyethylene sachet

Text in grey shading is optional for 10g

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nytox 1000 mg/g Powder for Solution for Fish Treatment in pouch [UK(NI)]
Cereka vet 1000 mg/g Powder for Solution for Fish Treatment in pouch [NO]

Tricaine methanesulfonate.

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

1 g of product contains 1000 mg of tricaine methanesulfonate.

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

<10g>
<50g>

4. ROUTE(S) OF ADMINISTRATION

Dissolution in water and subsequent topical application

5. WITHDRAWAL PERIOD(S)

Withdrawal period: 70 degree days after the end of treatment.
Fish must not be slaughtered for human consumption during treatment.
Do not use during stripping of fish eggs intended for human consumption.

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}
Once reconstituted use within 12 hours.

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Nytox 1000 mg/g Powder for Solution for Fish Treatment in pouch [UK(NI)]
Cereka vet 1000 mg/g Powder for Solution for Fish Treatment in pouch [NO]

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:

<[To be completed nationally]>

Manufacturer responsible for batch release:

Elara Pharmaservices Europe Ltd.
239 Blanchardstown Corporate Park
Ballycoolin
Dublin, D15 KV21
Ireland

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nytox 1000 mg/g Powder for Solution for Fish Treatment in pouch [UK(NI)]
Cereka vet 1000 mg/g Powder for Solution for Fish Treatment in pouch [NO]

Tricaine methanesulfonate.

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

This veterinary product is a white to off-white powder for solution for fish treatment, in a soluble pouch, for dissolution in water and subsequent topical application.

1 g of product contains 1000 mg of tricaine methanesulfonate, the active ingredient, and no other active ingredients or excipients.

4. INDICATION(S)

For use in an immersion bath for sedation, immobilisation and anaesthesia of fish for: vaccination, transportation, weighing, tagging, clipping, stripping of breed stock, blood-sampling and surgical procedures.

5. CONTRAINDICATIONS

Do not use with the following tropical fish species:
Apistogramma (Mikrogeophagus) ramirez, Balantiocheilos melanopterus, Etroplus suratensis, Melanotaenia maccullochi, Monodactylus argenteus, Phenacogrammus interruptus and *Scatophagus argus.*

Do not use in cases of known hypersensitivity to the active substance.

6. ADVERSE REACTIONS

None known.
If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

<Alternatively you can report via your national reporting system {national system details}.>

7. TARGET SPECIES

1. Ornamental fish, or their development stages, and
2. Breeding and juvenile stages of fish.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

An aqueous solution of the product is used in an immersion bath for sedation, immobilisation and anaesthesia of fish, both ornamental and those intended for human consumption.

The following examples of dose rates and exposure times are based on laboratory and field experience:-

		Concentration Mg/litre of water	Immersion time (mins)
Trout species (7-17ºC)			
Sedation		10-30	Up to 480
Anaesthesia	Light	30-80	Up to 30
	Deeper	80-180	Up to 10
Salmon species			
Sedation		7-30	Up to 240
Anaesthesia	Light	30-80	Up to 10
	Deeper	80-100	Up to 5
Bass species			
Sedation		8-30	Up to 480
Anaesthesia	Light	30-70	Up to 20
	Deeper	70-100	Up to 4
Carp species			
Sedation		20-30	Up to 1440
Anaesthesia		30-200	Up to 8
Fresh water tropical fish			
Sedation		30-50	Up to 1440

9. ADVICE ON CORRECT ADMINISTRATION

A number of factors influence the efficacy and safety of the product, including concentration of the drug in water, duration of exposure, temperature, oxygen and density of biomass. Because of these variable factors it is strongly recommended that a test of the selected drug concentration and exposure time is conducted with a small group of representative fish before large numbers are medicated, particularly when water temperature is at the upper or lower ends of the normal temperature ranges for the species being treated. The product should be dissolved in water of the same composition and characteristics as that to which the fish are accustomed.

Calculate the total number of water-soluble pouches required for the intended dosage of the immersion bath. Place up to five of these pouches into a labelled screw-topped polyethylene container, together with a quantity of water (2 litres or more of water). Screw the lid tightly onto the container and gently shake for 5 minutes before adding to the immersion bath. Effects on the fish should be monitored as the product is gradually introduced.

Before anaesthesia, or prolonged sedation, fish should be fasted for 12 to 24 hours. During treatment they should be stocked at a density not exceeding 80g/litre. To minimise damage and loss when medicated for long periods for transport etc. The level of sedation should allow fish to maintain their equilibrium and swimming position. Aeration should be provided unless sedation, or anaesthesia, is of

short duration. In anaesthesia loss of reflexes takes place in one to fifteen minutes after immersion depending upon concentration employed. Narcotised fish should be removed from medicated water and returned to their normal environment as soon as possible, when recovery will take between one and 30 minutes.

10. WITHDRAWAL PERIOD(S)

Withdrawal period: 70 degree days after the end of treatment.
Fish must not be slaughtered for human consumption during treatment.
Do not use during stripping of fish eggs intended for human consumption.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Store in a dry place.
Store in the original outer package.
Protect solution from direct sunlight.

Do not use this veterinary medicinal product after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Shelf life after reconstitution according to direction: 12 hours.

12. SPECIAL WARNING(S)

Special warnings for each target species:
None.

Special precautions for use in animals:
Do not exceed the dose recommended for each category of fish.

Brood stock anaesthetised for stripping should be immersed in unmedicated water immediately before collection of eggs or milt to avoid significant direct contact of either with the product.

As solutions of the veterinary medicinal product are slightly acidic, the use of phosphate or imidazole buffer has been proposed to reduce stress.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to tricaine methanesulfonate should avoid contact with the veterinary medicinal product.

Impermeable rubber gloves should be worn when handling the veterinary medicinal product.

Avoid contact with skin and eyes. In case of accidental contact, immediately wash the affected area with plenty of clean running water. If irritation persists, seek medical advice.

Handle the pouches carefully to avoid breaking them. Do not create dust when handling the product or preparing the anaesthetic solution. In case of accidental inhalation of dust, move to fresh air and if breathing is affected, seek medical advice immediately and show the package leaflet or the label to the physician.

In situations where dust is created when handling the product, wear a disposable half mask respirator conforming to European Standard EN 149 or a non-disposable respirator to European Standard EN 140 with a filter to EN 143.

Do not eat, drink or smoke whilst handling this product.

Wash hands after use.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Overdose (symptoms, emergency procedures, antidotes):
Remove fish immediately to aerated water of the same composition and temperature that is free from anaesthetic. Overdose or prolonged exposure to the product may cause respiratory failure and death.

Incompatibilities:
In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

Other Precautions:
In order to protect the environment, used solution must either be filtered using activated charcoal filters prior to dilution in the effluent to be discharged from the farm or it must be transferred to a holding tank filled with water with subsequent controlled release for dilution in the effluent to be discharged from the farm. See section 13 or further details.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Used solution must be transferred to a holding tank filled with water with subsequent controlled release for dilution in the effluent to be discharged from the farm.

Transfer of used solution to a holding tank filled with water and controlled release for dilution in effluent will ensure that the concentration of spent tricaine methanesulfonate in discharge water does not exceed 1 $\mu g \cdot L^{-1}$. When releasing the solution from the holding tank, flow rates are calculated based on the following equation:

$$\text{Discharge (L/hr)} = \frac{\text{Farm flow rate (L/min)} \times 0.90 \text{ (safety factor)}}{\text{Holding tank concentration (mg/L)} \times 1000} \times 60$$

Eg. Holding tank concentration (mg/L)	Farm flow rate (L/min)	Discharge flow from holding tank (L/h)
10	10,000 / 20,000 / 30,000	54 / 110 / 160
50	10,000 / 20,000 / 30,000	11 / 22 / 32
100	10,000 / 20,000 / 30,000	5.4 / 11 / 16
200	10,000 / 20,000 / 30,000	2.7 / 5.4 / 8.1

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

XXXXXXX

15. OTHER INFORMATION

Pack sizes for this product: 10g or 50g

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.