Sterilised Water for Injections

PL 20910/0007

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Sterilised Water for Injections

PL 20910/0007

LAY SUMMARY

The MHRA granted Taro Pharmaceuticals (Ireland) Limited, a Marketing Authorisation (licence) for the medicinal product Sterilised Water for Injections PL 20910/0007. This product is a Prescription only medicine used for the reconstitution, dilution and making-up of appropriate drugs where Sterilised Water for Injections is the diluent of choice, and for use as an irrigant.

Each 5 ml of solution contains 5 ml of sterilised water for injection and each 10 ml of solution contains 10 ml of sterilised water for injections.

The data presented to the MHRA, pre-licensing, demonstrated that Sterilised Water for Injections is essentially similar or equivalent to the approved product Water for Injections BP (PL 02848/5924R). Sterilised Water for Injections can therefore be used interchangeably with Water for Injections BP (PL 02848/5924R).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Sterilised Water for Injections outweighs the risk, hence a Marketing Authorisation has been granted.

Sterilised Water for Injections

PL 20910/0007

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation to Taro Pharmaceuticals (Ireland) Linited for the medicinal product Sterilised Water for Injections (PL 20910/0007) on the 21st of July 2006. This product is a prescription only medicine (POM).

This application was submitted as an abridged application according to article 10.1(a)(iii) of Directive 2001/83/EC claiming essential similarity to the original product Water For Injections BP (PL 02848/5924R).

Sterilised Water for Injections does not contain a drug substance and is used for the reconstitution, dilution and making-up of appropriate drugs where Sterilised Water for Injections is the diluent of choice, and for use as an irrigant.

PHARMACEUTICAL ASSESSMENT

Our Reference:	PL 20910/0007 - 0001
Product:	PL 20910/0007 TARO PHARMS IRELAND STERILISED WATER FOR INJECTIONS SOLUTION FOR INJECTION
Marketing Authorisation Holder:	TARO PHARMACEUTICALS (IRELAND) LIMITED
Active Ingredient(s):	WATER FOR INJECTIONS.
Type of Procedure:	National
Submission Type:	Initial
Submission Category:	Abridged
Submission Complexity:	Standard

1. INTRODUCTION

This is an abridged application for a Marketing Authorisation in the UK submitted under Article 10.1(a)(iii) of Directive 2001/83/EEC for a product claiming essential similarity to Water for Injections BP (PL 02848/5924R). The cross-referenced product was authorised to Antigen International Ltd on 20th July 1993.

1.1 Legal Status

Prescription only Medicine

3.2.S DRUG SUBSTANCE

Sterilised Water for Injections BP does not contain a drug substance.

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The drug product is a clear, colourless solution with the following composition:

Table1. Sterilised Water for Injection BP

Constituent	Quantity/5ml	Quantity/10ml	Quality
Water for injection	To 5ml	To 10ml	Ph. Eur.

3.2.P.2 Pharmaceutical Development

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation development

The water used in the manufacture of the finished product is distilled. A suitable method of sterilisation has been chosen.

There are no overages used in the manufacture of the product.

3.2.P.2.3 Manufacturing Process Development

Pilot batches of the drug product were manufactured. The maximum production batch size has been stated. The manufacturing process is described both in the description and in flow chart form. Comprehensive in-process controls are applied during manufacture. Essential stages of the manufacturing process have been validated using batches manufactured at the original manufacturing site. Batch analysis data has been provided.

3.2.P.2.4 Container Closure System

The drug product is filled into polypropylene ampoules, in 5ml or 10ml. The container closure system is constructed of materials typically used to package parenteral products. Based on stability data generated for the drug product, the container closure system is suitable for use.

3.2.P.2.5 Microbiological Attributes

Following sterilisation the polypropylene ampoules are checked for container integrity. Standard Ph. Eur. microbiological tests were carried out on the bulk and in-process samples during manufacture. Appropriate testing has been performed for the completed trial batches. All test results comply with test specifications.

3.2.P.2.6 Compatibility

The drug product is a diluent therefore its compatibility with other diluents is not relevant. Many pharmaceutical products can be diluted with Sterilsied Water for Injections, as long as the osmolarity, or the solubility and integrity of the pharmaceutical product are not affected.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacture

The manufacturer of the finished product is Taro Pharmaceuticals Ireland Limited.

3.2.P.3.2 Batch Formula

A formula is provided for the manufacturing of the commercial batch size for both the 5ml and 10ml ampoules. The commercial batch size for the 5ml ampoule fill size and for the 10ml batch size is stated.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

The manufacturing process and In-process controls are adequately described and are satisfactory.

3.2.P.3.4 Control of Critical Steps and Intermediates

At final volume, appropriate tests are carried out on the bulk solution Appropriate controls are in place for the critical process steps performed on the bulk solution.

3.2.P.3.5 Process Validation and/or Evaluation

A commitment has been provided to fully validate the manufacturing procedure during the manufacturing of the first commercial batches. Data on the validation of the trial batches confirming the uniformity of the solution have also been provided.

The process validation schedule for the commercial production batches is provided.

3.2.P.4 Control of Excipients

The specifications used are those presented in the Ph. Eur. It is stated that full monograph testing will be routinely performed.

Water for Injection in bulk is tested in accordance with Ph. Eur. methods. A Certificate of Analysis (COA) has been supplied.

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specification(s)

A satisfactory specification for the finished product has been provided. The product is tested according to the requirements of the BP/Ph.Eur. The test for extractable volume is performed according to the USP.

3.2.P.5.3 Validation of Analytical Procedures

Satisfactory data have been provided for the validation procedures. The validation test procedure is acceptable and compliant with Ph. Eur. method.

3.2.P.5.4 Batch Analyses

Batch analyses are presented for batches manufactured at the proposed site of manufacture. Each of the batches readily complies with the proposed finished product specification and a Certificate of Analysis has been presented for each batch.

3.2.P.5.6 Justification of Specification(s)

Compendial specifications and methods are used. The USP extractable volume test is used for the finished product.

3.2.P.6 Reference Standards or Materials

Not required.

3.2.P.7 Container Closure System

The primary packaging is polypropylene ampoules manufactured as part of the product filling process. The ampoules are hermetically sealed and are tamper proof. A label is attached to the front of each ampoule with adhesive stating the particulars of the product. The plastic is inert in respect to reaction with the product. The outer packaging is a cardboard carton. The Lot number and Expiry date are overprinted on the carton during packaging.

Schematic diagrams of the container closure system have been provided. COA from the polypropylene manufacturer and the COA from the contract laboratory have been provided. The tests have been performed in accordance with the Ph. Eur. monograph

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

Stability data have been provided on several batches under real-time and accelerated conditions to support the shelf-life.

A shelf life of 30 months is proposed for the finished product, at temperatures not exceeding 25°C.

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

A satisfactory protocol for post-approval stability studies has been provided. The applicant has stated commitment to place the first 3 commercial production batches under the stability studies with the protocol provided.

REGIONAL INFORMATION

A process validation scheme for the drug product has been supplied.

ASSESSOR'S COMMENTS ON MODULE I:

Summary of Product Characteristics (SPC)

The SPC is satisfactory and in line with the cross reference product's SPC.

Patient Information Leaflet

The PIL is satisfactory and in line with the cross reference product's PIL.

Label

The labels are satisfactory

Application Form

The application form is satisfactory

Comment on the Quality Overall Summary

The summary is satisfactory

ASSESSOR'S OVERALL CONCLUSIONS

This medicinal product can be granted a Marketing Authorisation.

PHARMACEUTICAL ASSESSOR

19th October 2005

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

PL NUMBER: **PL 20910/0007**
PRODUCT: **Sterilised water for injections**
ACTIVE: **Water for injection**
COMPANY: **Taro Pharmaceuticals Ltd**
LEGAL STATUS: **POM**

1.1. Introduction

This is an abridged application for a Marketing Authorisation in the UK submitted under Article 10.1(a)(iii) of Directive 2001/83 (as amended), first paragraph so called generic application.

The original product is water for injections BP first authorised on the 20th July 1993 to Antigen International Limited (PL 02848/5924R). No clinical studies have been performed.

A subsequent mutual recognition procedure is considered.

2. Indications

The applicant has submitted the following:

For the reconstitution, dilution and making-up of appropriate drugs where sterilised water for injections is the diluent of choice, and for use as an irrigant.

Water for injections has no pharmacological activity of its own and is used simply as a vehicle. The proposed indications are consistent with the original product and other water for injections products.

3. Dose and dose schedule

The dosage administered is dependent on the nature of the additive. The infusion rate will be dependent upon the dose regimen of the prescribed drug.
This is consistent with the original product and other water for injections products.

4. Toxicology

No formal data has been provided for this product and none are considered necessary. The non-clinical overview states that water for injections has no pharmacological efficacy and is simply used as a vehicle.

5. Clinical pharmacology

This application does not require the inclusion of a bioequivalence study as it is an essentially similar product for a parenteral product containing the same active substance and formulation as the reference product.

It has been stated that with the doses to be used with 5ml or 10ml ampoules no pharmacodynamic effects of the water will be seen and only excessive injection or infusion of water can result in water intoxication with disturbances of electrolyte balance, which is reasonable.

6. Efficacy

Water for injections has no pharmacological efficacy of its own and is used simply as a vehicle. No new data has been submitted and none required for this type of application.

7. Safety

The adverse event profile for water for injections is not considered to be a point of issue providing excessive administration is avoided, with adverse events being extremely rare. Water for injections is widely used and has a well defined safety profile. The data provided confirms the conclusion that the product has a benign safety profile.

The safety of the product is considered acceptable on the provision that it is of suitable quality and used as described in the SPC.

8. Clinical overview

The clinical overview has been completed by a suitably qualified clinician. The overview confirms that the sterilised water for injections has a satisfactory efficacy and safety profile with respect to the submitted therapeutic indications.

9. SPC

The SPC is acceptable

10. PIL

The PIL is in line with the SPC and is acceptable.

11. Label

The label is acceptable and in line with the medical components of the SPC.

12. MAA

The MAA is acceptable.

13. Conclusion

A marketing authorisation can be granted.

Medical Assessor

23rd November 2005

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for this application is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Water for injections has no pharmacological efficacy of its own and is used simply as a vehicle. No new data has been submitted and none required for this type of application.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is essentially similar to the cross-reference product and so interchangeable. The safety of the product is considered acceptable on the provision that it is of suitable quality and used as described in the SPC. Water for injections is widely used and has a well defined safety profile. The risk benefit is therefore considered to be positive.

Sterilised Water for Injections
PL 20910/0007

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on the 01/06/2005.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 12/08/2005.
3	Following assessment of the application the MHRA requested further information on the 15/11/2005, 13/03/2006, 05/04/2006, 21/04/2006 and on the 28/04/2006.
4	The applicant responded to the MHRA's requests, providing further information on 01/12/2005, 10/04/2006, 12/04/2006, 25/04/2006 and on the 10/05/2006.
7	The application was determined on 21/07/2006.

Sterilised Water for Injections
PL 20910/0007

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

Sterilised Water for Injections
PL 20910/0007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sterilised Water for Injections

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of solution contains 5 ml of sterilised water for injections.
Each 10 ml of solution contains 10 ml of sterilised water for injections.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless, odourless, solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the reconstitution, dilution and making-up of appropriate drugs where Sterilised Water for Injections is the diluent of choice, and for use as an irrigant.

4.2 Posology and method of administration

Route of administration: As appropriate to the reconstituted drug.
Dosage: The dosage administered will be dictated by the nature of the additive used. The administration rate will be dependent upon the dose regimen of the prescribed drug.
Following suitable admixture of prescribed additives, the dosage is usually dependent upon age, weight and clinical condition of the patient as well as laboratory determinations.

Administration
The solution is for dilution and delivery of the therapeutic additives. The directions for use related to the added medicinal product will dictate the appropriate volumes as well as the administration route.

4.3 Contraindications

Water for Injections should not be administered alone.
The contraindications related to the added medicinal product should be considered.

4.4 Special warnings and precautions for use

Water for Injections is hypotonic and should not be administered alone.
Do not use for intravenous injection unless adjusted to approximate isotonicity with a suitable solute.
When Water for Injections is used as a diluent for hypertonic solutions, appropriate dilution should be applied to bring the solution close to isotonicity.
Haemolysis may occur following infusion of large volumes of hypotonic solutions using sterile Water for Injections as a diluent
When administering large volumes, the ionic balance should be regularly monitored.
The large volume presentations (500 ml and 1000 ml) are for use as a bulk source of diluent in pharmacy compounding. They are not for direct intravenous administration.

4.5 Interaction with other medicinal products and other forms of interaction

None known.
The possible clinical interactions between the different medicinal products to be dissolved should be considered.

4.6 Pregnancy and lactation

The risks during use in pregnancy and in lactating women are determined by the nature of the added medicinal products.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Intravenous injections of Water for Injections may cause haemolysis if Water for Injections is administered alone.
The nature of the additive will determine the likelihood of any other undesirable effects.

4.9 Overdose

Haemolysis may occur following infusion of large volumes of hypotonic solutions using sterile water for injections as diluent.

The signs and symptoms of overdose will also be related to the nature of the medicinal product being added. In the event of accidental overdose, the treatment should be discontinued and the patient should be observed for the appropriate signs and symptoms related to the medicinal product administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: V07AB
group: solvents and diluting agents including irrigating solutions

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not applicable.

6.2 Incompatibilities

Sterilised Water for Injections should not be mixed with any other agents unless their compatibility has been established.

6.3 Shelf life

Unopened: 30 months.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Translucent polypropylene ampoules, 5 ml and 10 ml
Pack sizes: 20 x 5 ml ampoules, 20 x 10 ml ampoules

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Taro Pharmaceuticals Ireland Limited,
Lourdes Road,
Roscrea,
County Tipperary,
Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 20910/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/07/2006

10 DATE OF REVISION OF THE TEXT

21/07/2006

Patient Information Leaflet

Sterilised Water for Injections

Read all of this leaflet carefully before this product is used.
Keep this leaflet. You may need to read it again.
If you have further questions, please ask your doctor or pharmacist.
This product has been prescribed for you personally and you should not pass it on to others. It may harm them even if their symptoms are the same as yours.

In this leaflet:

This leaflet contains information on:
1. What **Sterilised Water for Injections** is and what it is used for
2. Before **Sterilised Water for Injections is used**
3. How to use **Sterilised Water for Injections**
4. Possible side effects
5. Storing **Sterilised Water for Injections**

Sterilised Water for Injections is a sterile solution for injection.
It contains water for injections. It does not contain an active ingredient or any other ingredients.

Marketing Authorisation Holder: Taro Pharmaceuticals Ireland Limited, Lourdes Road, Roscrea, County Tipperary, Ireland.

Manufacturer: Taro Pharmaceuticals Ireland Limited, Lourdes Road, Roscrea, County Tipperary, Ireland.

1. WHAT STERILISED WATER FOR INJECTIONS IS AND WHAT IT IS USED FOR

The name of the product is Sterilised Water for Injections, and it does not contain an active ingredient. It is a clear, colourless, sterile solution for injection, which comes in polypropylene ampoules of 5 ml and 10 ml. Each pack contains 20 ampoules.

Sterilised Water for Injections is called a diluent. It is used to prepare and dilute medicines that require mixing with water before they are injected. It is also used for irrigation (washing by a stream of liquid).

2. BEFORE STERILISED WATER FOR INJECTIONS IS USED

Do not use Sterilised Water for Injections:
The contraindications of the added product should be taken into account when using Sterilised Water for Injections.

Take special care with Sterilised Water for Injections:
- Sterilised Water for Injections should not be administered alone.
- It should not be used for intravenous injection unless the solution is adjusted to isotonicity with a suitable diluent.
- When used as a diluent for hypertonic solutions, the solution should be brought close to isotonicity.
- Haemolysis (disintegration of red blood cells) may occur if large volumes of hypotonic solutions using Sterilised Water for Injections as a diluent are given by intravenous infusion.
- When large volumes are given, the ionic balance should be monitored.
- Ensure that the container is undamaged and that the contents are clear and colourless.
- Solutions containing visible particles must not be used.
- No other medication and substance should be added to Sterilised Water for Injections unless compatibility is known.

Taking other medicines
Always tell your doctor if you are taking any other medicines because taking some medicines together can be harmful. Remember that the doctor at the hospital may not have been informed if you have recently begun a course of treatment for another illness.

Pregnancy
Ask your doctor or pharmacist for advice before you use this product or take any other medicine.

Breast-feeding
Ask your doctor or pharmacist for advice before you use this product or take any other medicine.

Driving and using machines
Sterilised Water for Injections is not expected to have any effect on the ability to drive and use machines.

3. HOW TO USE STERILISED WATER FOR INJECTIONS

When used to dilute or to dissolve a drug, follow the instructions of the drug to be administered. The method of administration (whether by injection into a muscle, into a vein or under the skin or by another route) will vary depending on the drug to which Sterilised Water for Injections has been added.

When used as an irrigant, the method of administration will depend on the irrigation procedure being used.

What to do in case of a missed dose:
If you think that you have missed a dose or that you have been given too much of this product, contact your doctor.

4. POSSIBLE SIDE EFFECTS

Intravenous injections of Sterilised Water for Injections may cause disintegration of red blood cells (haemolysis) if given alone. Also, side effects due to the drug to which it has been added may occur. Please consult the drug Patient Information leaflet for details of possible side effects. If you notice any unusual symptoms during or after treatment, tell your doctor or pharmacist.

5. STORING STERILISED WATER FOR INJECTIONS

Keep out of the reach and sight of children.
Do not store above 25°C.
Sterilised Water for Injections is for single use only. Use the product immediately after opening.
Discard any unused contents.
This product should not be used after the expiry (EXP) date printed on the pack.

6. FURTHER INFORMATION

For any further information about this product, please contact the local representative of the Marketing Authorisation Holder.

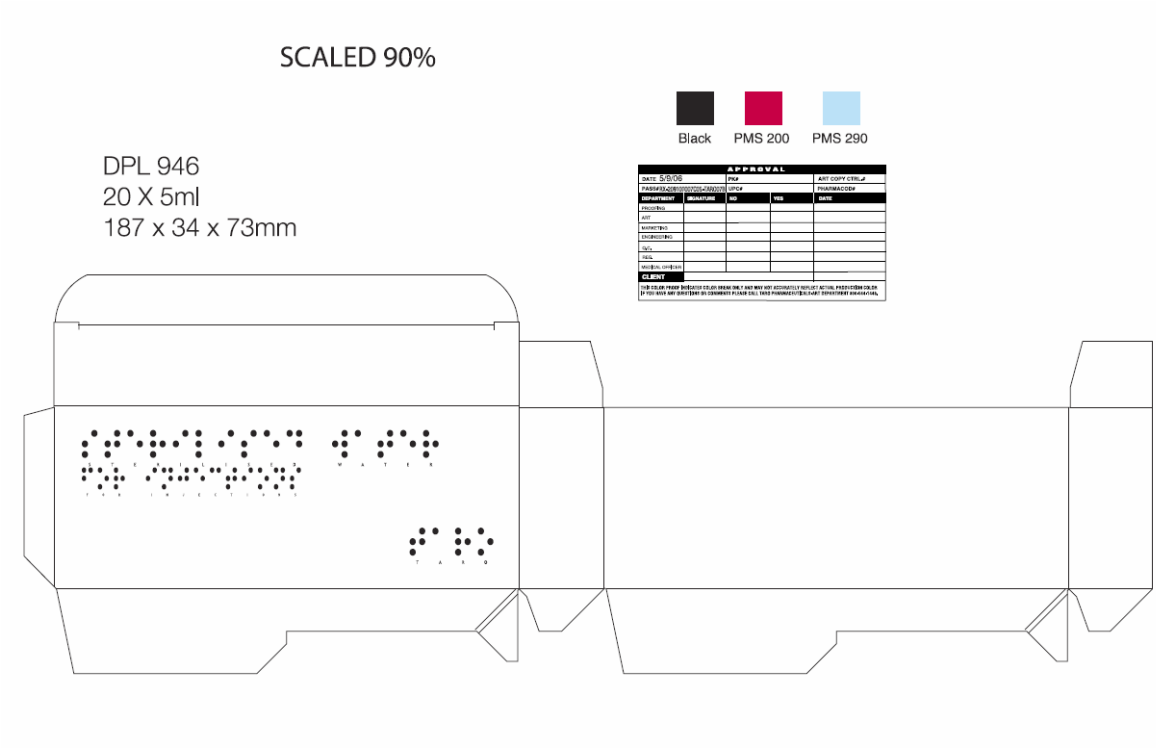
Taro Pharmaceuticals Ireland Ltd.,
Lourdes Road,
Roscrea,
County Tipperary,
Ireland.
Tel: + 353 (0) 505 24300
Fax: + 353 (0) 505 24310
info@taro.ie

This leaflet was last approved in MM/YYYY

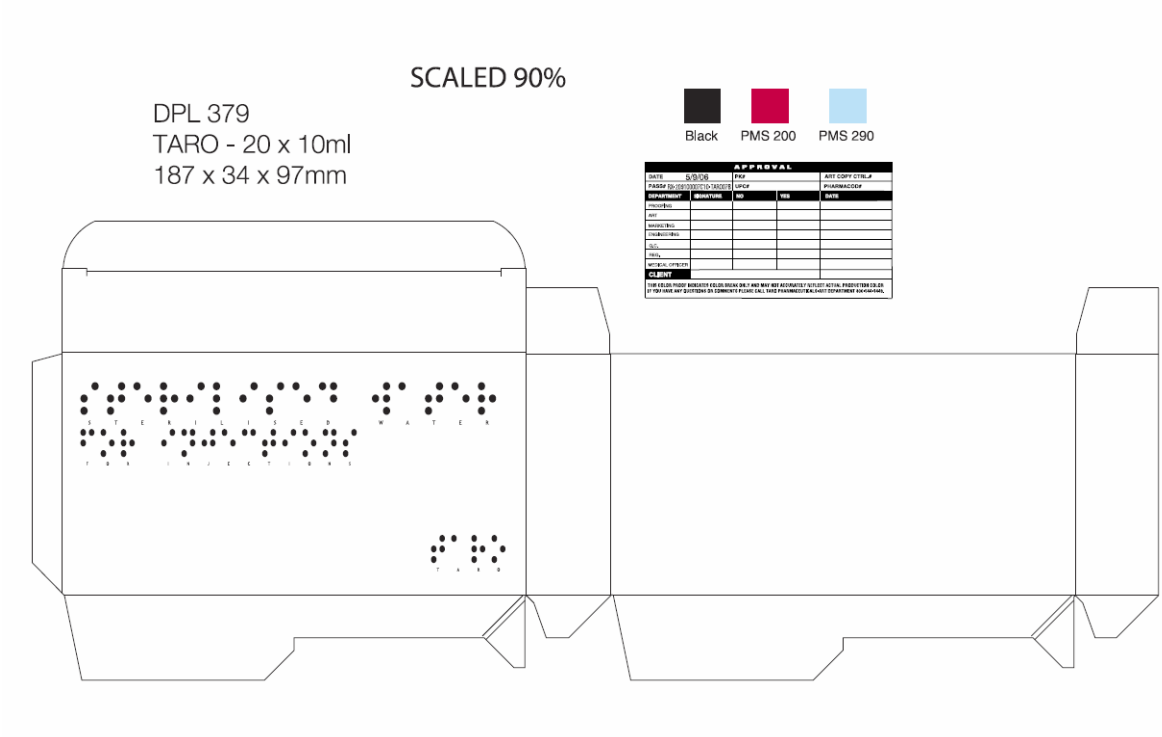
The leaflet text is available on CD for patients who have problems with their sight. It is available on request from Taro at the above address.

Marketing Authorisation Number: PL 20910/0007

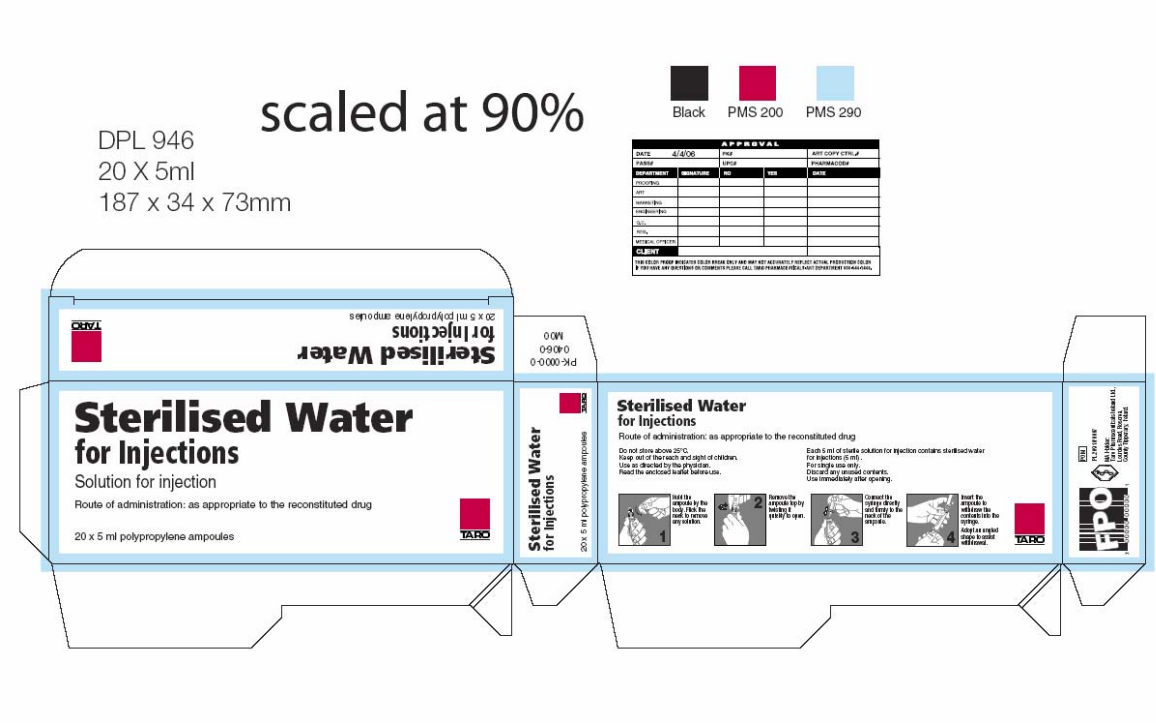
Sterilised Water for Injections
PL 20910/0007
Carton: Braille



Sterilised Water for Injections
PL 20910/0007
Carton: Braille



Sterilised Water for Injections
PL 20910/0007
Carton



Sterilised Water for Injections
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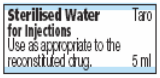
Carton

Sterilised Water for Injections
PL 20910/0007
Label



5ml 22 x 10mm

APPROVAL				
DATE 4/7/06		PK#		ART COPY CTRL.#
PASS#		UPC#		PHARMACOD#
DEPARTMENT	**SIGNATURE**	**NO**	**YES**	**DATE**
PROOFING				
ART				
MARKETING				
ENGINEERING				
Q.C.				
REG.				
MEDICAL OFFICER				
CLIENT				
THIS COLOR PROOF INDICATES COLOR BREAK ONLY AND MAY NOT ACCURATELY REFLECT ACTUAL PRODUCTION COLOR IF YOU HAVE ANY QUESTIONS OR COMMENTS PLEASE CALL TARO PHARMACEUTICALS-ART DEPARTMENT 800-544-1449.				

PMS Black

PMS 290

Sterilised Water for Injections
PL 20910/0007
Label

10ml 45 x 8mm

APPROVAL				
DATE 4/7/06		PK#		ART COPY CTRL.#
PASS#		UPC#		PHARMACOD#
DEPARTMENT	SIGNATURE	NO	YES	DATE
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ART				
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ENGINEERING				
Q.C.				
REG.				
MEDICAL OFFICER				
CLIENT				

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PMS Black

PMS 290