LIOTHYRONINE SODIUM 20 MICROGRAM INJECTION
PL 12762/0176

UKPAR

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LAY SUMMARY

The MHRA granted Goldshield Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Liothyronine Sodium 20 microgram Injection on 8th October 2007. This product, to be available by prescription only (POM), contains liothyronine sodium and is used for the treatment of severe thyroid gland deficiency (myxoedema), when it is not possible to give thyroid treatment by mouth.

The active ingredient liothyronine sodium is a form of thyroid hormone, which acts on the body to compensate for a lack of thyroid hormone function.

This application is a duplicate of a previously granted application for Triiodothyronine Injection 20 micrograms (PL 10972/0040) containing liothyronine as active ingredient, for which the marketing authorisation holder is Goldshield Group Plc and which was first authorised on 23rd August 1993.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Liothyronine Sodium 20 microgram Injection outweigh the risks, hence a Marketing Authorisation has been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Liothyronine Sodium 20 microgram Injection to Goldshield Pharmaceuticals Limited on 8th October 2007. The product is available as a prescription-only medicine (POM).

The application was submitted as a simple abridged application according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to Triiodothyronine Injection 20 micrograms (PL 10972/0040), approved on 23rd August 1993 to the marketing authorisation holder Goldshield Group Plc.

No new data were submitted nor were they necessary for this simple application, as the data are identical to that of the previously granted cross reference product. As the cross-reference product was granted prior to the introduction of current legislation, no PAR was generated for it.

The active ingredient liothyronine sodium is indicated for the treatment of myxoedema coma, usually in conjunction with other measures including the intravenous injection of a corticosteroid.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 12762/0176
PROPRIETARY NAME: Liothyronine Sodium 20 microgram Injection
ACTIVE(S): Liothyronine sodium
COMPANY NAME: Goldshield Pharmaceuticals Limited
E.C. ARTICLE: Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC
LEGAL STATUS: POM

1. INTRODUCTION

This is a simple, piggy back application for Liothyronine Sodium 20 microgram Injection submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Goldshield Pharmaceuticals Limited, NLA Tower, 12-16 Addiscombe Road, Croydon, Surrey, CR0 0XT.

The application cross-refers to Triiodothyronine Injection 20 micrograms (PL 10972/0040), approved on 23rd August 1993 to the marketing authorisation holder Goldshield Group Plc. The current application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed name of the product is Liothyronine Sodium 20 microgram Injection. The product has been named in-line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The product contains liothyronine sodium, equivalent to 20 micrograms. It is to be stored in glass vials with a bromobutyl rubber in pack sizes of 5 vials. The proposed shelf-life (12 months) and storage conditions ('Store below 25 degrees' and 'Keep container in the outer carton') are consistent with the details registered for the cross-reference product.

2.3 Legal status

On approval, the product will be available as a prescription-only medicine (POM).

2.4 Marketing authorisation holder/Contact Persons/Company

Goldshield Pharmaceuticals Limited, NLA Tower, 12-16 Addiscombe Road, Croydon, Surrey, CR0 0XT.

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in-line with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
No materials of animal or human origin are included in the product. This is consistent with the cross reference product.

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts' CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed summary is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/CARTON
PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

Carton and blister
The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In-line with current legislation, the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with the application are acceptable. A Marketing Authorisation should be granted.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

As this is a duplicate application, no new clinical data have been supplied and none are required.

OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT

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

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

EFFICACY
This application is identical to a previously granted application for Triiodothyronine Injection 20 micrograms (PL 10972/0040).

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.

BENEFIT RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product. Extensive clinical experience with liothyronine sodium is considered to have demonstrated the therapeutic value of the compound. The benefit:risk is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 04/09/2003
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 28/10/2003.
3	Following assessment of the application the MHRA requested further information on 28/01/2004.
4	The applicant responded to the MHRA's requests, providing further information on 23/08/2004
5	The application was determined on 08/10/2007

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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

LIOTHYRONINE SODIUM 20 MICROGRAM INJECTION
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Liothyronine Sodium 20 micrograms Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 20 micrograms liothyronine sodium
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Intravenous injection
Packed as a freeze dried white plug, in a glass vial for reconstitution with 1 or 2ml water for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Liothyronine Sodium Injection is indicated for the treatment of myxoedema coma, usually in conjunction with other measures including the intravenous injection of a corticosteroid. For the treatment of less severe forms of myxoedema and for maintenance therapy, orally administered liothyronine should be used.

4.2 Posology and method of administration
Dosage:
5 to 20 micrograms given by slow intravenous injection, and repeated at intervals of 12 hours or less if required. The minimal interval between dosing is 4 hours. An initial dose of 50 micrograms intravenously is used by some physicians, followed by further intravenous injections of 25 micrograms every 8 hours until improvement occurs. The dosage may then be reduced to 25 micrograms intravenously twice daily.

Method of Administration:
Usually given by intravenous injection, as the alkalinity of the solution may cause irritation of the tissues if given by deep intramuscular injection. The solution is prepared by adding 1 or 2ml water of injection to the ampoule, and shaking gently until the solution has dissolved.

4.3 Contraindications
Hypersensitivity to any components of the preparation. Liothyronine sodium is contraindicated in patients with cardiovascular disorders or angina of effort.

4.4 Special warnings and precautions for use
Liothyronine must be given with extreme cautionin myxoedema coma because too large a dose can precipitate heart failure, especially in elderly patients and those with ischaemic heart disease. ECG monitoring can give a useful indication of impending ishcaemia, however, changes in ST segment can be confused with similar changes occurring in hypothyroidism. In severe and prolonged hypothyroidism, there may be decreased adrenocortical activity. When thyroid replacement therapy is started, metabolism is raised at a greater rate that adrenocortical activity and this can result in adrenocortical insufficiency. This insufficiency may require supplemental adrenocortical steroids. Thyroid replacement therapy may cause an increase in the dosage requirement of insulin or other anti-diabetic treatment. Care is needed in patients with diabetes mellitus and diabetes insipidus.

4.5 Interaction with other medicinal products and other forms of interaction
Liothyronine sodium therapy may potentiate the action of anticoagulants. Anticonvulsant, such as carbamazepine and phenytoin-enhance the metabolism of thyroid hormones and may displace thyroid hormones from plasma proteins. Initiation or discontinuation of anticonvulsant therapy may alter liothyronine dose requirements. Phenytoin levels may be increased by liothyronine.

Liothyronine raises blood sugar levels and this may upset the stability of patients receiving antidiabetic agents. If co-administered with cardiac glycosides, adjustment of dosage of cardiac glycoside may be necessary.

Liothyronine increases receptor sensitivity to catecholamines thus, accelerating the response to tricyclic antidepressants. A number of drugs may affect thyroid function tests and this should be borne in mind when monitoring patients on liothyronine therapy.

Co-administration with oral contraceptives may result in an increased dosage requirement of liothyronine sodium.

4.6 Pregnancy and lactation

Pregnancy:
The safety of liothyronine during pregnancy is not known. Any possible risk of congenital abnormalities must be weighed against the risk to the foetus of untreated hypothyroidism in the mother.

Lactation:
Liothyronine is excreted into breast milk in low concentration. This may interfere with neonatal screening programmes.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The following are indicative of overdosage, and disappear after reduction of dosage or stopping treatment for a day or more:
Anginal pain, cardiac arrhythmias, palpitations, cramps, tachycardia, diarrhoea, restlessness, excitability, headache, flushing, sweating, excessive loss of weight and muscular weakness.

4.9 Overdose

Overdose may present as an exaggeration of the side-effects, as well as agitation, confusion, irritability, hyperactivity, headache, sweating, mydriasis, tachycardia, arrhythmias, tachypnoea, pyrexia, increased bowel movements and convulsions.

Treatment is symptomatic. In adults, tachycardia has been controlled by 40mg propanolol every six hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Liothyronine (L-triiodothyronine) is a naturally occurring thyroid hormone. Its biological action is qualitatively similar to that thyroxine, but the effect is more rapid in onset (in a few hours) and the effect disappears within 24 to 48 hours after stopping treatment.

5.2 Pharmacokinetic properties

Liothyronine is less readily bound to plasma proteins than thyroxine, and about 0.5% exists in the unbound form. The half-life in the blood is about one to two days in euthyroidism. Thyroid hormones do not readily cross the placenta. Minimal amounts are reported excreted in breast milk.

5.3 Preclinical safety data

No additional data.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dextran 110, freeze dried
Sodium Hydroxide
Water for Injection

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
12 months

6.4 Special precautions for storage
Do not store above 25°C.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container
3ml hydrolytic clear glass vial with bromobutyl stopper containing 20 micrograms of Liothyronine Sodium in a freeeze-dried, sterile white plug, packed into a carton containing 5 vials.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Goldshield Pharmaceuticals Limited
NLA Tower
12-16 Addiscombe Road
Croydon
Surrey CR0 0XT
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 12762/0176

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
08/10/2007

10 DATE OF REVISION OF THE TEXT
08/10/2007

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

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Goldshield

PATIENT INFORMATION LEAFLET

Liothyronine® Sodium 20 micrograms Injection

Please read this leaflet carefully before you start to take your medicine.
This leaflet does not contain all the information about your medicine.
If you have any questions, or you are not sure about anything, ask your doctor or pharmacist.

THE NAME OF YOUR MEDICINE IS:
Liothyronine® Sodium 20 micrograms Injection

THE ACTIVE INGREDIENT IS:
Liothyronine sodium.
This medicine is a sterile injection for administration into a vein. 20 micrograms of liothyronine sodium is packed as a freeze-dried white plug in a neutral glass vial for reconstitution with 1 or 2 ml of water for injections. It is available as 5 vials of 20 micrograms liothyronine sodium in a carton pack.

WHAT ELSE IS IN YOUR MEDICINE?
As well as liothyronine sodium, this medicine contains dextran 110 freeze dried, sodium hydroxide.

This medicine is a naturally occurring thyroid hormone.

Product Licence Holder and Company Responsible for Manufacture: Goldshield Pharmaceuticals Ltd., NLA Tower, 12-16 Addiscombe Road, Croydon, Surrey, CR0 0XT, UK,

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WHAT IS YOUR MEDICINE USED FOR?
Your medicine is given, by injection into a vein (intravenously), for the treatment of severe thyroid gland deficiency (myxoedema), when it is not possible to give thyroid treatment by mouth. It is usually given in conjunction with an intravenous corticosteroid. For the treatment of less severe forms of myxoedema, and for maintenance treatment, orally administered liothyronine or thyroxine are used.

BEFORE YOU ARE GIVEN YOUR MEDICINE:
You should not receive this injection if,
- You are allergic to thyroid preparations or to other ingredients in this injection.
- You have a disease involving heart or blood vessels (cardio-vascular disease)
- You have angina pectoris (pain in the chest due to insufficient blood supply to the heart)

Please inform your doctor if you have any of the above conditions.

If the answer to any of the following questions is YES, or you are not sure about the answers, tell your doctor or pharmacist.

- Do you have heart failure (e.g. suggested by symptoms like swelling of the ankles, breathlessness etc.) or you are being treated with Cardiac glycosides e.g. digoxin (to treat the heart).
- Do you have diabetes or you are taking anti-diabetic drugs?
- Are you being treated with any of the following:
  - Anticoagulants (to thin the blood)?
  - Anticonvulsants (to control fits) (e.g. Carbamazepine or Phenytoin)?
  - Anti-depressants (e.g. Tricyclic antidepressants)?
- Are you taking any other drugs not listed above?
- If female, are you taking a contraceptive pill, are you pregnant, or are you breast feeding?
- Are you over 65 years of age?

This medicinal product contains less than 1 mmol sodium (23mg) per dose i.e. essentially sodium-free.

WHAT PRECAUTIONS SHOULD YOU TAKE?
- You will have to lie down to be given this medicine.
- The medicine will be given into the vein by slow injection.
- You may have your heart monitored (by ECG) when this medicine is given to you.
- This medicine is for single use only. The remaining solution should be discarded after use.

TAKING YOUR MEDICINE:
- The medicine will have been diluted with sterile water for injections.
- The usual dose is 5 to 20 micrograms given by slow intravenous injection. This dose may be repeated at intervals of 12 hours, or less, if required. The minimum interval between doses is four hours.
- Some physicians may use a starting dose of 50 micrograms, and subsequent doses of 25 micrograms.

AFTER HAVING YOUR MEDICINE:
As with all medicines, this medicine may cause unwanted effects in some people.
If you experience any of the following, tell your doctor.
- Pain in your chest (angina)
- Irregular heart beat
- Palpitations
- Cramps
- Rapid heart beat
- Diarrhoea
- Restlessness
- Excitability
- Headache
- Flushing
- Sweating
- Excessive loss of weight
- Muscular weakness

If you experience any other unwanted effects not listed, tell your doctor or pharmacist.

PRECAUTIONS:
- Do not store above 25°C. Keep the vial in the outer carton in order to protect from light.
- Your medicine would have been made fresh each time.
- Keep out of the reach and sight of children
- Not to be used after the "Expiry Date" printed on the pack.

If you have any questions about the use of this medicine, ask your doctor.

Date of partial revision: May, 2007

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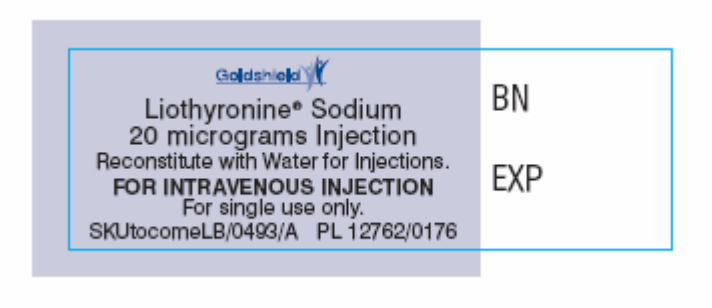
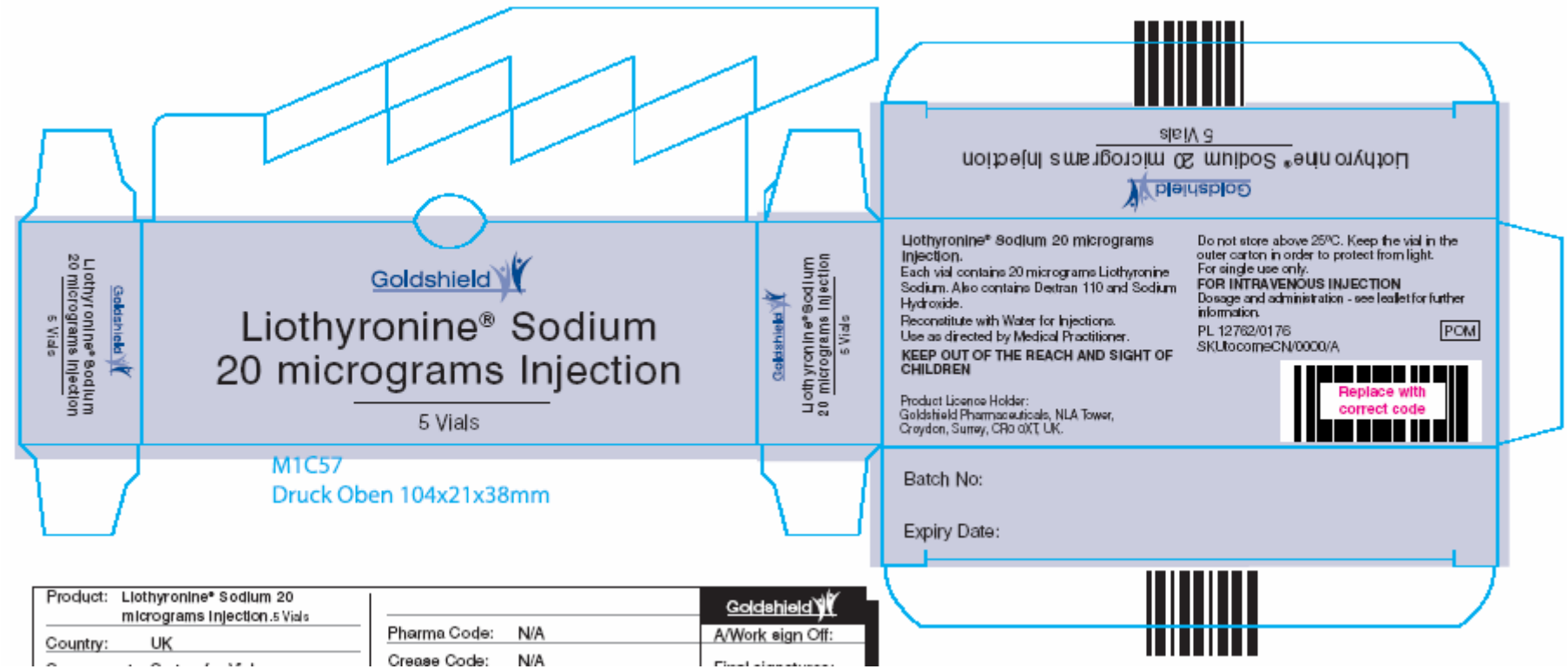
LABELLING




Goldshield
Liothyronine® Sodium
20 micrograms Injection
5 Vials
M1C57
Druck Oben 104x21x38mm
Liothyronine® Sodium 20 micrograms Injection
5 Vials
Liothyronine® Sodium 20 micrograms Injection.
Each vial contains 20 micrograms Liothyronine Sodium. Also contains Dextran 110 and Sodium Hydroxide.
Reconstitute with Water for Injections.
Use as directed by Medical Practitioner.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Product Licence Holder:
Goldshield Pharmaceuticals, NLA Tower, Croydon, Surrey, CR0 0XT UK.
Do not store above 25ºC. Keep the vial in the outer carton in order to protect from light.
For single use only.
FOR INTRAVENOUS INJECTION
Dosage and administration - see leaflet for further information.
PL 12762/0176
SKUtocomeCN/0000/A
POM
Replace with correct code
Batch No:
Expiry Date:
Product: Liothyronine® Sodium 20 micrograms Injection.5 Vials
Country: UK
Pharma Code: N/A
Crease Code: N/A
A/Work sign Off: