

Ginkgoforce Ginkgo biloba tablets

THR 13668/0016

UKPAR

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GINKGOFORCE GINKGO BILOBA TABLETS

THR 13668/0016

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bioforce (UK) Ltd a Traditional Herbal Registration certificate for the traditional herbal medicinal product Ginkgoforce Ginkgo biloba tablets (Traditional Herbal Registration number: THR 13668/0016). This product is available without prescription and can be bought from pharmacies and other outlets.

The active ingredient of Ginkgoforce Ginkgo biloba tablets comes from the leaves of the tree *Ginkgo biloba* L. *Ginkgo biloba* leaf is a traditional herbal medicine used to relieve the symptoms of Raynaud's syndrome and tinnitus. This registration is based exclusively upon the longstanding use of *Ginkgo biloba* leaf as a traditional herbal medicine and not upon data generated from clinical trials. There is no requirement under the Traditional Herbal Registration scheme to prove scientifically that the product works.

No new or unexpected safety concerns arose from this application and it was, therefore, decided that a Traditional Herbal Registration Certificate could be granted.

GINKGOFORCE GINKGO BILOBA TABLETS

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted a Traditional Herbal Registration Certificate for the traditional herbal remedy Ginkgoforce Ginkgo biloba tablets (Traditional Herbal Registration number: THR 13668/0016) to Bioforce (UK) Ltd on 15 May 2009. This product is on the general sales list (GSL).

This application was submitted according to Article 16.c of Directive 2001/83 EC, as amended, as part of the Traditional Herbal Medicines Registration Scheme.

The data supplied by the applicant demonstrate 30 years of traditional use of *Ginkgo biloba* in the European Community. A satisfactory review of the available safety data on *Ginkgo biloba* has also been provided, together with an expert report supporting the proposed product.

PHARMACEUTICAL ASSESSMENT

HERBAL SUBSTANCE: GINKGO BILOBA

Latin name: *Ginkgo biloba* L.
Common name: Ginkgo, Maidenhair tree, Fossil Tree
Family: Ginkgoaceae
Parts of plant used: Leaf
Cultivation area: Central Europe

Background information

Ginkgo is the world's oldest living species of tree, originating in China and introduced into Europe in the 1700s. *Ginkgo biloba* is the only surviving member of the family. The plant can grow up to 30 metres tall and has distinctive fan-shaped leaves. All ginkgo leaves are sourced from cultivation and there is no threat of extinction of *Ginkgo biloba* as a species according to the WWF.

Manufacture

The herbal substance is collected from cultivated trees in Central Europe (France and Switzerland) under organic conditions (according to EC Directive 2092/91) and in accordance with Good Agricultural and Collection Practice (GACP) guidelines.

The leaves are harvested by hand from the beginning of August until October over a maximum of two days. They are filled into net bags and stored in a cooling chamber under controlled conditions. If no cold-storage room is available then leaves of only one harvesting day are supplied.

Control of Herbal Substance

An appropriate specification based on the Ph Eur monograph is applied and is acceptable. The specification is supported by the batch data provided.

Reference Standards or Materials

Suitable certificates of analysis have been provided for the reference substances used.

Container Closure System

The herbal substance is packed into net bags and kept in a cooling chamber with a controlled temperature. If no cold-storage room is available then leaves of only one harvesting day are supplied. The bags are transported in a cooled truck to the herbal preparation manufacturer within one day.

Stability

No stability data are provided. Given that the herbal substance is collected over a maximum period of two days, stored and transported within one day, and processed immediately, stability data are not considered necessary.

HERBAL PREPARATION: GINKGO BILOBA DRY ETHANOLIC EXTRACT

General Information

Scientific name of the plant:	<i>Ginkgo biloba</i> L.
Drug: extraction solvent ratio (DER):	3-5:1
Extraction solvent:	Ethanol 60% m/m

The herbal preparation is a fine coarse, light to dark brown, aromatic hygroscopic powder.

Manufacture

A satisfactory description of the manufacturing process of the herbal preparation has been provided.

The in-process controls are satisfactorily detailed. There are no critical steps identified as the manufacture of the herbal preparation is considered a standard procedure.

Certificates of analysis for all materials used in the manufacture of the herbal preparation have been provided.

Control of Herbal Preparation

A satisfactory specification with appropriate tests and limits has been provided for the herbal preparation.

Satisfactory analytical procedures are used to control the quality of the herbal preparation. Analytical procedures have been validated, as appropriate.

Certificates of analysis have been provided for production batches of the herbal preparation, demonstrating satisfactory compliance with the proposed specification.

The proposed specification has been justified satisfactorily.

Reference Standards or Materials

Suitable details have been provided for the reference standards used.

Container Closure System

The herbal preparation is stored in an appropriate container. A declaration has been provided confirming that this container is suitable for storage of foodstuffs

Stability

Stability studies have been carried under ICH conditions. The results support the proposed shelf life of the herbal preparation.

HERBAL PRODUCT: GINKGOFORCE GINKGO BILOBA TABLETS

Description and Composition of the Herbal Product

The product is a brown-speckled round, biconvex, bevelled tablet containing 90 mg of native dry ethanolic extract of fresh *Ginkgo biloba* L. leaf (DER 3-5:1).

The tablets contain the excipients microcrystalline cellulose, magnesium stearate and soya polysaccharide. The choice of excipients is based on experience and compatibility of the chosen excipients with the active substance is confirmed by stability testing. All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of soya polysaccharide, in the absence of a European Pharmacopoeial monograph for excipient this is satisfactory

Magnesium stearate is confirmed to be sourced from plant origin. There are no overages in this product.

Manufacture

A description and flow-chart of the manufacturing method has been provided. The manufacturing method is a standard uncomplicated procedure of direct tableting.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on product batches and the results are satisfactory.

Control of Herbal Product

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification.

Reference Standards or Materials

Suitable details have been provided for the reference standards used.

Container Closure System

The finished product is packed in amber class III glass bottles (35ml and 60ml) with an aluminium pilfer proof closure fitted with a polyethylene liner. The bottle is inserted into a cardboard outer carton with a patient information leaflet.

Specifications and certificates are provided from the manufacturers for all components. It is confirmed that all components comply with the Ph. Eur and / or are suitable for use with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a product shelf-life of 36 months with the storage condition "Store in the original container" is appropriate.

Assessor's comments on the Summary of Product Characteristics, label and Patient Information Leaflet

All product literature is satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured

and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY

The grant of Traditional Herbal Registrations is acceptable.

NONCLINICAL ASSESSMENT

NONCLINICAL ASPECTS

The Expert Safety Report submitted by the applicant lists relevant references to published work studying the toxicology of *Ginkgo biloba*.

NONCLINICAL OVERVIEW

The applicant has submitted a literature review with this application. An Expert Safety Report was provided, which included reviews of some non-clinical data. The Expert Safety Report was written by experts with expertise in pharmacology and toxicology. The report is dated December 2006.

The overview submitted in support of this application is satisfactory.

Due to a shortage of published data on *Ginkgo biloba*, it is not possible to assess if the safety package for the phytochemical constituents of *Ginkgo biloba* is acceptable to the standards of today's GLP and safety testing requirements. However, the information supplied demonstrating traditional use is acceptable and thus the lack of provision of a complete standard safety package is acceptable and in compliance with guideline EMEA/HMPC/32116/05.

In view of the absence of results of genotoxicity testing the applicant has provided assurance that results will be provided before the renewal of the registration.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC for this product is satisfactory from a preclinical point of view.

ENVIRONMENTAL RISK ASSESSMENT

An environmental risk assessment is not required for herbal medicinal products according to guidance CPMP/SWP/4447/00.

CONCLUSION

The information supplied demonstrates the traditional use of *Ginkgo biloba*. An adequate literature review of *Ginkgo biloba* has been carried out by the applicant and no new non-clinical data was submitted for assessment with this application. Granting of a THR is acceptable.

CLINICAL ASSESSMENT

PROPOSED INDICATION

The applicant has proposed the following:

“A traditional herbal medicinal product used to relieve the symptoms of Raynaud's syndrome and tinnitus, based on traditional use only.”

The proposed indication is acceptable.

EVIDENCE OF LONG-STANDING USE

Article 16 c 1 (c) requires the Applicant to provide bibliographic or expert evidence to show that the medicinal product in question, or a corresponding product, has been in medicinal use throughout a period of at least 30 years, including at least 15 years within the Community.

A full literature review has been submitted, along with a comprehensive summary and discussion of the literature provided. The Applicant has provided evidence for the use of Ginkgo within the EU for a period exceeding 30 years. Bioforce have marketed *Ginkgo biloba* tincture since 1987.

SAFETY REVIEW

Article 16 c 1 (D) requires the Applicant to provide a bibliographic review of safety data, together with an expert report.

A safety review has been provided and an Expert Report.

The applicant has undertaken an adequate safety summary. The most frequent adverse events encountered are related to the gastrointestinal system.

PRODUCT LITERATURE

The product literature (Summary of Product Characteristics, Patient Information Leaflet and labelling) for this product are medically satisfactory.

ASSESSMENT OF SUITABILITY FOR GSL STATUS FOR GINKGO BILOBA

Section 51 of the Medicines Act 1968 states that “GSL may be appropriate for medicines which can, with reasonable safety, be sold or supplied otherwise than by or under the supervision of a pharmacist”. The term “reasonable safety” may usefully be defined as: “Where the hazard to health and the risk of misuse and the need for special precautions in handling are small, and where wider sale would be a convenience to the purchaser”.

Suitability of indication for GSL:

1. Hazard to health

There appears to be a low risk of hazard to health in the proposed indication.

2. Risk of misuse

There appears to be minimal risk of misuse of this product is felt to be low.

3. Need to take special precautions in handling

No special precautions required.

4. Wider sales are convenient to the purchaser

This would apply.

In summary, it is considered that the four above mentioned criteria have been met and this product may be suitable for GSL status.

DISCUSSION

The data supplied by the Applicant demonstrate 30 years of traditional use within the European Community required for registration under the Traditional Herbal Medicines Product Directive. A satisfactory review of the available safety data relating to *Ginkgo biloba* has been provided together with an expert report supporting the registration of the product.

RECOMMENDATIONS

A Traditional Registration may be granted.

OVERALL CONCLUSION AND RISK ASSESSMENT

QUALITY

Bioforce (UK) Ltd has over 30 years of experience in manufacturing herbal medicinal products. The quality data submitted with this application are satisfactory.

PRECLINICAL

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

EFFICACY AND SAFETY

No clinical efficacy data are required for registration of Traditional Herbal Medicinal Products (THMP).

The Applicant has provided a bibliographic review which shows ample evidence for the use of *Ginkgo biloba* within the EU for a period exceeding 30 years.

The SPC, PIL and labelling are satisfactory.

RISK ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk: benefit ratio is, therefore, acceptable.

GINKGOFORCE GINKGO BILOBA TABLETS

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STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the Traditional Herbal Registration application on 4 April 2007
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 9 August 2007
- 3 This application was discussed at a HMAc (Herbal Medicines Advisory Committee) meeting and, as a result, the MHRA requested further information relating to the quality, non-clinical and clinical dossiers on 31 January 2008
- 4 The applicant responded to the MHRA's requests, providing further information on the dossiers on 9 October 2008
- 5 Following assessment of the response the MHRA requested further information relating to the quality dossier on 13 March 2009
- 6 The applicant responded to the MHRA's requests, providing further information on the quality dossier on 6 April 2009
- 7 A THR was granted on 15 May 2009

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ginkgoforce Ginkgo biloba tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 90 mg of extract (as dry extract) from *Ginkgo biloba* L. fresh leaf (3-5:1). Extraction solvent: Ethanol 60% m/m.

Excipients:

One tablet contains 12.5 mg soya polysaccharide

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

It is a brown speckled, round, biconvex, bevelled tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

A traditional herbal medicinal product used to relieve the symptoms of Raynaud's syndrome and tinnitus, based on traditional use only.

4.2 Posology and method of administration

Adults and the elderly: One tablet twice daily after food increasing to two tablets twice daily if necessary.

Children and adolescents less than 18 years old:

The use in children and adolescents under 18 years of age is not recommended (see Section 4.4).

Duration of use:

If the symptoms worsen or persist for more than 4 weeks a doctor or a qualified healthcare practitioner should be consulted.

For oral use only.

4.3 Contraindications

Do not use in cases of known hypersensitivity to Ginkgo preparations or to any of the excipients.

This product contains soya polysaccharide. If you are allergic to peanut or soya, do not take this product. Refer to Section 2, for soya polysaccharide content.

4.4 Special warnings and precautions for use

The use in children and adolescents under 18 years of age is not recommended because data are not sufficient and medical advice should be sought.

Keep out of the reach and sight of children.

There are rare case reports of spontaneous bleeding in association with the use of products containing *Ginkgo* extracts. Although no causal link has been established care should be taken by patients who have a pre-existing bleeding disorder. It is advisable that Ginkgoforce tablets are discontinued at least 2 weeks prior to surgery or that clotting parameters are assessed prior to surgery.

4.5 Interaction with other medicinal products and other forms of interaction

Appropriate studies have not been conducted to determine whether drug interactions occur with Ginkgoforce and its active constituents.

4.6 Pregnancy and lactation

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been undertaken.

4.8 Undesirable effects

The following adverse reactions have rarely been reported in association with the use of products containing *Ginkgo* extract.

Body as a whole – general disorders

- Allergy

Central and peripheral nervous system disorders

- Headache

Gastrointestinal system disorders

- Nausea
- Vomiting
- Diarrhoea

Skin and appendages

- Pruritis
- Rash

There have been very rare case reports of Stevens-Johnson syndrome associated with the use of *Ginkgo* extract.

There are sporadic case reports of bleeding disorders in patients who have been taking preparations containing *Ginkgo* extract. The causality in these cases is not established.

4.9 Overdose

No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.

5.2 Pharmacokinetic properties

Not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.

5.3 Preclinical safety data

The preclinical toxicology data available are limited.

An *in vitro* study has shown the aqueous ethanolic *Ginkgo* extract used in this product to be non-mutagenic in the *Salmonella typhimurium* reverse mutation assay up to the dose of 5,000 µg/plate.

Tests on reproductive toxicity and carcinogenicity have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Magnesium stearate
Soya polysaccharide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in the original container.

6.5 Nature and contents of container

Amber glass bottles (type III) with aluminium pilfer proof closure fitted with a polyethylene liner.

Pack sizes: 60 tablets
120 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

- 7 MARKETING AUTHORISATION HOLDER**
Bioforce (UK) Ltd,
2 Brewster Place,
Irvine
KA11 5DD, UK
Telephone: 01294 277344
enquiries@avogel.co.uk
- 8 MARKETING AUTHORISATION NUMBER(S)**
THR 13668/0016
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**
15/05/2009
- 10 DATE OF REVISION OF THE TEXT**
15/05/2009

PATIENT INFORMATION LEAFLET



Patient Information Leaflet

A.Vogel

Ginkgoforce[®]
Ginkgo biloba tablets



Information

Important things you need to know

- This product is used to relieve the symptoms of Raynaud's syndrome and tinnitus.
- This product is suitable for adults over 18 years.
- **Don't take** this product if you are allergic to peanut, soya or any of the ingredients: see section 6.
- **Before you take this product:** read section 2.
- **Dosage instructions:** see section 3.
- **Talk to your doctor** if your symptoms worsen or do not improve within 4 weeks.
- Side effects are minor and rare: see section 4.

Now read the rest of this leaflet carefully. Keep this leaflet. You may need to read it again.

1. What this product is for

Ginkgoforce is a traditional herbal medicinal product used to relieve the symptoms of:

- Raynaud's syndrome
 - Cold hands and feet
 - Pain, tingling or numbness in the extremities
- Tinnitus (ringing in the ears)

This is based on traditional use only.

What is Raynaud's syndrome?

Raynaud's syndrome is a condition where the blood supply to the fingers and toes is interrupted in response to changes in temperature or emotional stress. This causes the skin to turn white and can cause pain, numbness or tingling. This usually affects the fingers and toes.

Do's & Don'ts

2. Before you take this product

Do not take this product:

- If you are under 18 years of age.
- If you are **allergic** to:
 - Ginkgo products.
 - Peanut or soya. This product contains soya polysaccharide.
 - Any of the other ingredients in this product. (See section 6 Further Information)
- If you are pregnant or breast-feeding.
- If you have been told by your doctor that you have a bleeding disorder. This means you have a tendency to bleed for longer than is normal.
- If you are due to have an operation in the next 14 days.

Using

3. How to take this product

Adults and the elderly: Take 1 tablet twice daily after food. The dose can be increased to 2 tablets twice daily if necessary.

Not for use in children or those under 18.

For oral use only. Don't take more than the recommended dose.

If you take more of this product than you should

- If you take too much and feel ill, talk to your doctor. Taking too much is unlikely to be harmful.

If you forget to take this product

- Don't worry about the missed dose. Take the next dose as usual.

If you feel this product isn't working

- See your doctor if your symptoms worsen or do not improve within 4 weeks.

Please turn over...

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Side effects

4. Possible side effects

Like all medicines, this product can cause side effects, although not everybody gets them.

Minor side effects

The following minor side effects can occur when using this product. These are rare and likely to affect less than 1 in 1,000 people.

Digestive symptoms

- Feeling sick (nausea)
- Digestive upsets such as sickness or diarrhoea

These are often short-lived and should get better on their own. However if they persist, talk to your doctor or pharmacist.

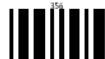
Skin reactions

- Itching (pruritis)
- Rash

Other side effects

- Allergic reactions
- Headache

Stop taking the product if any of these occur.



There have been very rare reports of the following occurring after the use of Ginkgo extracts:

- Blistering of the skin and mucous membranes (Stevens-Johnson syndrome)
- Bleeding disorders

It is not known if these were caused by Ginkgo. If you experience them seek medical advice and take this leaflet with you.

If you are concerned about any side effect or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Information

5. How to store this product

- Keep out of the reach and sight of children.
- Do not use this product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.
- Store in the original container.
- Do not use this product if you notice a change in colour. The tablets should be speckled brown in colour.

6. Further Information

What this product contains

1 tablet contains 90 mg of extract (as dry extract) from *Ginkgo biloba* L. fresh leaf (3–5:1). Extraction solvent: ethanol 60% m/m.

The other ingredients used for the tablet are microcrystalline cellulose, soya polysaccharide and magnesium stearate (vegetable source).

What this product looks like and the contents of the pack

The tablets are round and speckled brown in colour. This product is available in packs containing 60 and 120 tablets. Not all pack sizes may be marketed.

Traditional Herbal Registration Holder and Manufacturer

Traditional Herbal Registration Holder and Batch Release:

Bioforce (UK) Ltd,
2 Brewster Place,
Irvine, Ayrshire, UK
KA11 5DD

Manufacturer:

Bioforce AG, CH-9325, Roggwil
Switzerland

THR No. 13668/0016

This leaflet was approved on MM/2009

What is Ginkgo biloba?

Ginkgo biloba is native to China and is the oldest living tree species. The leaves are used to produce Ginkgoforce tablets.

You should also know

Bioforce runs a helpline by phone and email which can provide you with further information.

Email: enquiries@avogel.co.uk

Phone: 0845 608 5858

You can get a larger print or audio version of this leaflet.

Call this number:
0845 608 5858.

LABELLING

Label (60 tablet pack):

Ginkgoforce is a traditional herbal medicinal product used to relieve the symptoms of Raynaud's syndrome and tinnitus. This is based on traditional use only.

Directions for use:

Adults and the elderly: Take 1 tablet twice daily after food. The dose can be increased to 2 tablets twice daily if necessary.

Not for use in children or those under 18. For oral use only. Read leaflet before use. Keep out of the reach and sight of children. Store in the original container.



Traditional Herbal Registration Holder:
Bioforce (UK) Ltd, Irvine, UK, KA11 5DD
THR No. 13668/0016



Ingredients: 1 tablet contains 90 mg of extract (as dry extract) from *Ginkgo biloba* L. fresh leaf (3–5:1). Extraction solvent: ethanol 60% m/m. The other ingredients used for the tablet are microcrystalline cellulose, soya polysaccharide and magnesium stearate (vegetable source). This product contains soya polysaccharide. Do not use if you are allergic to soya or peanut. See leaflet for further information.

Batch:

EXP:

30440L1 9266300

Carton (60 tablet pack):



Label (120 tablet pack):

Ginkgoforce is a traditional herbal medicinal product used to relieve the symptoms of Raynaud's syndrome and tinnitus. This is based on traditional use only.

Directions for use:

Adults and the elderly: Take 1 tablet twice daily after food. The dose can be increased to 2 tablets twice daily if necessary.

Not for use in children or those under 18. For oral use only. Read leaflet before use. Keep out of the reach and sight of children. Store in the original container.



Traditional Herbal Registration Holder:
Bioforce (UK) Ltd, Irvine, UK, KA11 5DD
THR No. 13668/0016



Ingredients: 1 tablet contains 90 mg of extract (as dry extract) from *Ginkgo biloba* L. fresh leaf (3-5:1). Extraction solvent: ethanol 60% m/m. The other ingredients used for the tablet are microcrystalline cellulose, soya polysaccharide and magnesium stearate (vegetable source). This product contains soya polysaccharide. Do not use if you are allergic to soya or peanut. See leaflet for further information.

Batch:

EXP:

30440L1 9266300

Carton (60 tablet pack):

