

ATROGEL ARNICA GEL

THR 13668/0009

UKPAR

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ATROGEL ARNICA GEL

THR 13668/0009

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bioforce (UK) Limited a Traditional Herbal Registration Certificate for the traditional herbal medicinal product Atrogel Arnica Gel (Traditional Herbal Registration number: THR 13668/0009). This product is available without prescription and can be bought from pharmacies and other outlets.

The active ingredient of Atrogel Arnica Gel is an extract obtained from the fresh flower heads of the *Arnica montana* plant. Atrogel Arnica Gel is a traditional herbal medicinal product used for the symptomatic relief of muscular aches, pains and stiffness and sprains, bruises and swelling. The registration is based exclusively upon the longstanding use of Arnica flowers 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.

ATROGEL ARNICA GEL

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted a Traditional Herbal Registration Certificate for the traditional herbal remedy Atrogel Arnica Gel (THR 13668/0009) to Bioforce (UK) Limited on 30 October 2006. This product has been granted a general sales licence (GSL).

This application was submitted as a standard application 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 Arnica products in the European Community. A satisfactory review of the available safety data on *Arnica montana* has also been provided, together with an Expert Report supporting the proposed product.

PHARMACEUTICAL ASSESSMENT REPORT

I REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

None.

II INTRODUCTION

This is a national application submitted by Bioforce (UK) Ltd under the Traditional Herbal Medicines Registration Scheme.

The manufacturer of the herbal substance has provided a satisfactory GMP certificate of compliance. The site was inspected by a competent authority.

A satisfactory certificate of GMP compliance has been provided by the manufacturer of the finished herbal product. The site was inspected by a competent authority.

The distributor is Bioforce (UK) Ltd at 2 Brewster Place, Irvine, Ayrshire KA11 5DD, UK. Bioforce (UK) is the importer with the Qualified Person, although Bioforce (AG) in Switzerland is the site of quality control analysis. The current manufacturing import licence is provided.

The product is currently registered in Switzerland under the same product name.

There are several herbal and homeopathic products containing Arnica licensed by the MHRA which were granted licences following the review of their Product Licence of Rights (PLR) and one herbal product which was given a product licence under Article 10(c) as an informed consent application.

Legal status

A General Sales List status has been granted for the product. Arnica is currently on GSL Schedule 1 for External use only.

Use

A traditional herbal medicinal product for the symptomatic relief of muscular aches, pains and stiffness, sprains, bruises and swelling after contusions, exclusively based on long-standing use.

III.A HERBAL SUBSTANCE

III.A.1 General information

Scientific name of plant: *Arnica montana* L.

Synonyms: Arnicae flos

German name: Arnika

English name: Arnica

Parts of the plant: Fresh, flower-heads *Arnica montana*: Flos rec.

Arnica montana L. flowers are yellow and 5-8 cm in diameter. The seeds are black, slender-lanceolate, pointed, 5-8 mm long, with pappus hairs about 8 mm long. It is very typical for Arnica that two additional flowering heads are located mostly in the axils of the two upper leaves under the uppermost, terminal flowering heads. The herbaceous plant is perennial, up to 0.5 m high, with short, thick rhizome. The entire plant has an aromatic odour. The leaves are oval to

lanceolate and have an entire margin (no lobes or teeth). The basal leaves form a rosette. The stem leaves are opposite with narrowed base and are sessile.

The characteristic constituents of *Arnica montana* L. flower-heads are:

- Sesquiterpene lactones (SL) of the pseudo-guaianolide type (principally helenalin and 11a, 13-dihydrohelenalin and their esters with acetic, isobutyric, methacrylic, tiglic and other carboxylic acids)
- Flavonols, flavonol glycosides, flavonol glucuronides
- Kaempferol-3-glucoside (astragalin): Mr = 448.3; C₂₁H₂₀O₈
- Diterpenes
- Arnidiol (a triterpene)
- Caffeic acids and derivatives
- Polyacetylenes
- Coumarines
- Fatty acids
- Essential oils
- Pyrrolizidine alkaloids (tussilagine and isotussilagine)

III.A.2 Manufacture

Manufacturer

Bioforce AG at CH-9325 Roggwil, Switzerland

Description of Manufacturing Process and Process Controls

Cultivation and harvest

Arnica montana L is cultivated organically, thus without pesticides. Neither treatment with fumigation agents nor with ionising radiation occurs after harvesting as the herbal material is processed in the fresh state and the storage time is kept short in order to avoid any deterioration of the medicinal herb. The fresh Arnica flower-heads must be delivered to the production plant of Bioforce AG within a suitable time limit after harvesting.

Transport takes place under cool-conditions. After delivery, the fresh herbal material is processed within the specified time limit (which varies depending on the storage temperature). Storage time and conditions have been validated and are checked as IPC during the manufacturing process. Cultivation is done in accordance with the Guideline on agricultural and collection practice for starting materials of herbal origin (GACP), this is satisfactory.

III.A.3 Characterisation

The identification of the plant material includes the thin layer chromatography (TLC) test on *Calendula officinalis* and *Heterotheca inuloides* in compliance with the Ph Eur monograph. Further impurities in the herbal substance such as microbial contamination, heavy metals and pesticides are included in the specification. As the fresh plant is used without storage the risk of aflatoxin contamination is minimal and the justification is acceptable.

III.A.4 Control of Herbal Substance

Specification

The specification of the herbal substance/material has been provided by the applicant and is MHRA PAR; ATROGEL ARNICA GEL, THR 13668/0009

satisfactory.

Certificates of analysis for two batches of the fresh *Arnica montana* flowers have been provided.

III.A.5 Reference Standards or Materials

Please see section III.B.5.

III.A.6 Container Closure System

Not described.

III.A.7 Stability

Manufacturing validation has shown the maximum time that flowers stored at different temperatures can be kept. Bioforce requires that its farmers deliver the flowers and the flowers are processed within the validated time periods.

III.B HERBAL PREPARATION

III.B.1 General information

Herbal preparation: *Arnica montana*: Flos rec. T.

Scientific name of the plant: *Arnica montana* L. (Synonym: *Arnicae flos*)

Parts of the plant used: Fresh flower-heads

Herbal - Extraction solvent - Ratio (DER)

Extraction solvent: Ethanol 50.0 % (m/m)

Description of the herbal preparation: clear liquid, with dark yellow to green-yellow colour and aromatic, fresh odour.

The herbal preparation in Atrogel is an ethanol tincture of the fresh flower-heads of *Arnica montana* L. (*Arnica montana*: Flos rec. T.). The tincture is manufactured by maceration, using ethanol 50.0 % (m/m) as solvent.

III.B.2 Manufacture

Manufacturer

The herbal preparation, *Arnica montana*: Flos rec. T., is manufactured by Bioforce AG, 9325 Roggwil, Switzerland.

Description of Manufacturing Process and Process Controls

A satisfactory description and flow-chart of the manufacturing method has been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on full-scale batches of the product. The results are satisfactory.

Control of Materials

The starting materials are as listed below:

Starting materials	Function	Reference
<i>Arnica montana</i> L	Herbal substance	Ph Eur monograph for <i>Arnicae flos</i> and Ph Eur general monograph for herbal drugs.
Purified water	Extraction solvent	Ph Eur
Ethanol 94% m/m	Extraction solvent	Ph Eur

Please also see section III.A.4 Control of Herbal Substance.

Ethanol 96% and purified water are in compliance with the Ph Eur monograph and certificates of analysis have been provided from Bioforce AG.

Controls of Critical Steps and Intermediates

The in-process controls (IPC) are provided and are satisfactory.

A risk analysis has been performed on each step of the manufacturing process.

Manufacturing Process Development

The manufacturing process development has been adequately described. Bioforce AG has over 30 years of experience in manufacturing fresh plant tinctures.

III.B.3 Characterisation

Please see section III.A.3

III.B.4 Control of Herbal Preparation

Specification

Details of the release specification for *Arnica montana*: Flos rec. T. are provided along with its shelf life specification and both are satisfactory.

Analytical Procedures

The analytical methods are detailed and are satisfactory.

Validation of Analytical Procedures

Satisfactory validation of the assay by the HPLC method has been provided. Satisfactory validation of the method for the determination of ethanol by GC has been provided.

Batch Analyses

Certificates of analysis (CoA) are provided for two batches of the herbal preparation *Arnica montana*: Flos rec. T. manufactured in 2001 and 2004 and released by Bioforce AG. The results

indicate little variation between the batches. Certificates of analysis of three recent batches of the herbal preparation are provided and are satisfactory.

III.B.5 Reference Standards or Materials

Certificates of Analysis of the standards used are provided. The identity and purity of both compounds have been sufficiently established. The reference substances used for the identification tests, namely Rutin *R* (rutoside), chlorogenic acid *R*, hyperoside *R* and caffeic acid *R* comply with the requirements of the Ph Eur.

III.B.6 Container Closure System

Arnica montana: Flos rec. T. is stored in a suitable container closure system. A description of the container closure system and its specifications are provided. The stability data provided in section 3.2.S.7 show no incompatibilities between the drug substance and the container.

III.B.7 Stability

Two batches of herbal preparations stated to be production batches have been subjected to stability testing in ICH long term and accelerated conditions. Stability testing was carried out in the containers as described above. The batches are tested using the methods defined in the stability specification. Microbial quality is tested every 12 months.

The studies have been fully completed to the proposed duration of 36 months in long term conditions and for 9 months in accelerated conditions.

The results support the proposed shelf life of 24 months. As only two batches of data have been provided, the manufacturer has committed to place a third production-scale batch of the active substance in a stability study (under long-term storage conditions according to ICH) as soon as the next production takes place, this is in accordance with CPMP/QWP/122/02, rev 1.

IV HERBAL PRODUCT

IV.1 Description and Composition of the Herbal Product

Atrogel is a clear, golden-brown to green yellow gel for topical use.

Qualitative composition of the drug product.

Ingredients	Function	Reference standard
Drug substance:		
<i>Arnica montana</i> : Flos rec. T.	drug substance	In-house
Excipients:		
Ethanol 94% (m/m)	filler, solvent	Ph Eur
Purified water	filler, solvent	Ph Eur
Glycerol 85% (m/m)	moisturizer	Ph Eur
Hypromellose	thickener	Ph Eur

Type of container:

Atrogel is packed in a white laminated multilayer polyethylene tube (with vapour block layer (SiO_x-layer). The opening of the tube is sealed with an aluminium peel-seal. The closure is a polypropylene screw cap. The pack size is 100 ml.

IV.2 Pharmaceutical Development

Ethanol is used for microbial stability and to adjust the ethanol content in the gel to 50% m/m, identical to the ethanol concentration of the tincture used. Glycerol acts as a moisturiser and hypromellose is chosen to control the viscosity of the final product. The product was tested in order to optimise its colour, viscosity and homogeneity. A satisfactory description of the development method has been provided, where the optimal blending time for the mixing of the herbal substance with the excipients was investigated to achieve homogeneity of the bulk and the packaged product. The compatibility of Atrogel with the primary packaging was checked, focusing on the volatility of ethanol during a defined storage period. As the finished product contains 50% m/m ethanol, a preservative efficacy test was performed and results demonstrate that the final product (and herbal preparation) complies with the requirements of the preservation test according to the Ph Eur for topical products.

IV.3 Manufacture

Manufacturer

The finished product is manufactured by a suitable manufacturer and a manufacturing authorisation has been provided.

The quality control is stated to be at Bioforce AG at 9325 Roggwil, Switzerland and the batch release site of the herbal product is at Bioforce (UK) Ltd in 2 Brewster Place, Irvine, Ayrshire KA11 5DD, UK.

Batch Formula

The batch formula has been provided as follows:

Qualitative batch formula of the drug product.

Names of Ingredients	Reference to Standards
<i>Herbal preparation</i>	
<i>Arnica montana</i> : Flos rec. T.	In-house
Excipients: Ethanol 94 % (m/m) Purified water Glycerol 85 % (m/m) Hypromellose	Ph Eur Ph Eur Ph Eur Ph Eur

Description of Manufacturing Process and Process Controls

The gel is manufactured by directly mixing the herbal preparation (*Arnica montana*: Flos rec. T.) with the excipients.

A satisfactory description and flow-chart of the manufacturing method has been provided.

Critical steps have been identified and in-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on full-scale batches of the product.
The results are satisfactory.

IV.4 Control of Excipients

Specifications

All the excipients and analytical procedures are as specified in Ph Eur monographs. Certificates of analysis (CoA) of the excipients have been provided by the suppliers. The raw material used in the manufacture of glycerol is of vegetable origin and, therefore, does not present any risk of TSE/BSE contamination. Ethanol 94% m/m used to manufacture the finished product is of the same quality as that used as a solvent for the extraction of the herbal substance.

IV.5 Control of Herbal Product

Specification(s)

The release and shelf-life specifications of the drug product are provided and are satisfactory.

Analytical Procedures

The tests for pH, viscosity and microbial quality are in accordance with the Ph Eur. The TLC method is analogous to the Ph Eur monograph for Arnica flowers and the assay by HPLC method is developed in-house. The method and validation for the determination of ethanol is as previously described under the herbal preparation.

Validation of Analytical Procedures:

Validation of the assay by HPLC method

The assay is carried out by determination of Marker 2 in the finished product. The method has been validated satisfactorily for precision, linearity, accuracy, specificity and robustness.

Batch Analyses

Certificates of Analysis (CoA) have been presented for two batches of the finished drug product from Bioforce AG.

IV.6 Reference Standards or Materials

The reference standards used in the identification test by TLC are of Ph Eur standard CoAs have been provided for marker substances by the suppliers and identity and purity sufficiently established.

IV.7 Container Closure System

Atrogel is packed in a white laminated multilayer polyethylene tube. The opening of the tube is sealed with an aluminium peel-seal. The closure is a polypropylene screw cap. Content of the container/pack size: 100 ml.

Details of specifications set by the finished product manufacturer for the primary closure system are provided. A statement confirming that the polyethylene and polypropylene raw materials

comply with the Ph.Eur. monograph 3.1.3 (5th edition) is provided.

IV.8 Stability

Stability Summary and Conclusion

Stability studies were carried out on three pilot scale batches under ICH conditions in long term and accelerated conditions. Stability testing was carried out in containers similar to those proposed for marketing apart from a slight difference in the length of the nozzle of the tube neck (5 mm longer) and the composition of outer layer of the tube (not in contact with the drug product) where the type of plastic material has been changed. The batches were tested according to specifications for shelf-life. The limits applied are in accordance with the release specifications. The studies have been fully completed to their proposed durations: 36 months' data from the long term studies, 6 months' data from the accelerated studies and end-of-use plus 2 months' data from the in-use stability studies have been provided.

The results support the proposed shelf life of 24 months. Neither an in-use nor special storage conditions have been proposed and this is acceptable based on the results provided. During the course of the application the manufacturer has placed one production scale batch under stability study and also committed to place two further production-scale batches on stability studies.

Adventitious Agents Safety Evaluation

Bioforce AG has confirmed that no excipients have been used which are of animal origin and that glycerol (85%) is of vegetable origin. As a consequence there exists no risk of transmitting animal spongiform encephalopathy by the finished product.

V. ASSESSOR'S COMMENTS ON THE SUMMARY OF PRODUCT CHARACTERISTICS, LABEL AND PATIENT INFORMATION LEAFLET

Summary of Product Characteristics (SPC)

The SPC for this product is satisfactory.

Patient Information Leaflet (PIL)

The PIL has undergone User Testing (UT). The results of the UT and final PIL have been submitted and are satisfactory.

Labelling

Colour mock-ups of the labels have been provided, including the Braille text for the name 'Atrogel'. All labelling is satisfactory.

VI. ADMINISTRATIVE

Comment on the Quality Overall Summary

The quality overall summary provided a balanced discussion of the quality part of the dossier.

THR form

The THR Application (THR) form submitted with this application is satisfactory.

VII. ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY

A grant of a Traditional Herbal Registration is acceptable.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

1. INTRODUCTION

This is a national application submitted by Bioforce (UK) Ltd under Article 16.c of Directive 2001/83 EC, as amended (Traditional Herbal Medicines Registration Scheme). The product is a gel preparation for cutaneous use containing an ethanolic tincture of the fresh flower-heads of *Arnica montana* L., where 1g of the gel contains 500mg of tincture.

A number of Arnica products are currently authorised for external use and the products are all GSL products.

Atrogel was approved as an OTC medicine in Switzerland in April 2003. It has been marketed in the EU since September 2001 and is on the market in the Netherlands, Ireland, Finland, Denmark and the UK.

2. BACKGROUND

The genus Arnica belongs to the family Compositae (daisy family).

The drug substance, Atrogel, is an ethanolic tincture of the fresh flowers of Arnica Montana L. (*Arnica Montana*; Flos rec. T.). By virtue of the manufacturing method, the tincture employed is considered to be a primary (total) extract.

According to the ESCOP (2003) monograph on ‘‘Arnicae Flos’’, the characteristic constituents of *Arnica Montana* L. flowerheads are:

-Sesquiterpene lactones (SL) of the pseudo-guaianolide type

Flavonols

Kaempferol- -3 glucoside (astragalín)

Diterpenes

Arnidol (a triterpene)

Caffeic acids and derivatives

Polycytacetylenes

Coumarines

Fatty acids

Essential oils

Pyrrolizidine alkaloids (tussilagine and isotussilagine) in trace amounts and are considered to be non-toxic as they lack the 1,2 unsaturated necin groups (Pabreiter, C. et al, 1992).

Constituents with known therapeutic activity are not known. Therefore the genuine extract, i.e. the tincture of the fresh Arnica flowerheads, is considered to be the active substance in Atrogel.

The fresh herbal material employed for Atrogel is cultivated organically (cert. organic farming) in central Europe.

3. PROPOSED INDICATION

The applicant has proposed the following:

A traditional herbal medicinal product for the symptomatic relief of muscular aches, pains and
MHRA PAR; ATROGEL ARNICA GEL, THR 13668/0009

stiffness, sprains, bruises and swelling after contusions, exclusively based on long-standing use.

Assessor's Comment

This is satisfactory.

4. DOSE & DOSE SCHEDULE

Adults: Apply 2 - 10 cm gently to the affected area 2 to 4 times daily.

Children and the elderly: Apply similarly as described for adults (above).

For cutaneous use only.

Assessor's Comment

The dosage of Atrogel complies with both the Commission E and ESCOP monographs and the excipients raise no safety concerns.

5. TOXICOLOGY

No toxicology data is required for applications under EC Article of Directive 2001/83/EEC.

6. EFFICACY

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

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

6.1 EVIDENCE OF TRADITIONAL USE

Arnica is generally accepted to have a tradition of use as an herbal medicine.

Assessor's Comments

There is ample evidence of traditional use of *Arnica montana* for a period exceeding 30 years for the treatment of bruising, sprains and injuries. Therefore, a Traditional Herbal Registration can be granted for these indications.

5. SAFETY REVIEW

Article 16 c 1 (D) requires the Applicant to provide bibliographic safety data together with an expert report. A safety review and Expert Report are provided. The Clinical Review of Safety submitted in the dossier outlines adverse events from controlled and uncontrolled studies relevant to the safety of arnica.

5.1 Adverse events

There are a number of case studies documenting skin reaction to the use of *Arnica montana* herb or extracts which range in severity from itchy erythema to contact dermatitis in a delayed type of allergic reaction.

Contraindications and cautions for use

There is no evidence for topical arnica to be contraindicated with any oral medicines.

Skin sensitivity or skin allergies to arnica herb are the most commonly reported adverse events associated with arnica therapy. These reactions are self-limiting and almost all are mild to moderate in severity. Therefore it would be prudent for those with known sensitivity to plants in the Compositae (Asteraceae) family to avoid the using arnica extracts.

Post Marketing Experience

Periodic Safety Update

All reported events were considered to be mild to moderate severity and transient.

Clinical Conclusion on PSUR Data

Local skin irritation and skin allergies appear to be the most common adverse events associated with topical *Arnica montana* and topical arnica preparations. Almost all reported adverse reactions to topical arnica were of mild to moderate severity.

It would be prudent for those with known sensitivity to plants in the Compositae family to avoid the using arnica extracts.

Assessor's Comments

The Updated UK Drug Analysis Print (DAP) to 26/05/06 lists all spontaneously reported reactions on the ADROIT database associated with arnica. The most commonly reported of these were skin and subcutaneous reactions: rash, rash maculo-papular, swelling face, pruritus. All were from single constituent products. There were no deaths associated with these reported reactions to arnica.

The number and type of adverse reactions to arnica in the UK MHRA DAP is similar to the PSUR submitted by the applicant and are an additional indication of the rarity of adverse reactions to the substance.

These give no cause for safety concerns in addition to what is already described in the submission dossier.

Global Analysis of Safety

In addition to the above, there are a number of bibliographic references spanning a period of traditional use of *Arnica Montana* flower-heads. It is recognised that its use should be confined to topical application as ingestion may cause gastro-intestinal irritation. However the pre-clinical data indicates LD₅₀ values with a sufficient margin of safety following normal topical use of Atrogel and traditionally the herb has been used safely when applied topically.

There have been no reports in the literature or in PMS of the reported adverse reactions being anything other than self-limiting and transient. However, there is a markedly higher incidence of adverse events in those with known allergies to the Compositae family of plants. Therefore arnica is not recommended for use in this group.

There is little safety data available on the use of Arnica/Atrogel in pregnancy or lactation. It should be used only under the supervision of a medical practitioner in pregnancy. There is no evidence to suggest that the product should not be used during lactation.

The SPC includes information taking account of the known safety profile of topical arnica.

Medical Assessor's Overall Comment on Safety

The safety data submitted, including, a clinical study, bibliographic reviews, PSUR and Global Safety Analysis, suggest that Atrogel is unlikely to cause any specific safety concerns as an OTC topical medication.

Allergic skin reactions are the most common side effects. The incidence is similar to those with topical ibuprofen.

It should not be recommended to those known to be sensitive to plants of the *Compositae* family of plants. It should not be used in pregnancy unless under the guidance of a medical practitioner as there is no data available on the use of topical Arnica in pregnancy.

6. SUMMARY OF PRODUCT CHARACTERISTICS

The SPC for this product is satisfactory.

7. PATIENT INFORMATION LEAFLET

The PIL for this product is satisfactory.

8. LABELLING

The labelling is satisfactory.

9. DISCUSSION

This is an application for registration under the Traditional Herbal Medicinal Products Directive. The data supplied by the Applicant are sufficient to demonstrate 30 years of traditional use of Arnica within the European Community for corresponding products. A satisfactory review of the available safety data on *Arnica montana* has been provided together with an Expert Report supporting the proposed product.

10. RECOMMENDATIONS

A Traditional Herbal Registration Certificate may be granted.

OVERALL CONCLUSION AND RISK ASSESSMENT

QUALITY

Bioforce AG has over 30 years of experience in manufacturing fresh plant tinctures. 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 *Arnica montana* 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.

ATROGEL ARNICA GEL

THR 13668/0009

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the Traditional Herbal Registration application on 9 January 2006
- 2 Following assessment of the application the MHRA requested further information relating to the quality dossier on 2 May 2006 and the clinical dossier on 7 July 2006
- 3 The applicant responded to the MHRA's requests, providing further information on the clinical dossier on 3 October 2006 and the quality dossier on 27 October 2006
- 4 The application was determined on 30 October 2006

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atrogel Arnica Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g gel contains:

500 mg extract (as liquid extract) of fresh Arnica Flowers (*Arnica montana* L.)
(equivalent to 120 - 200 mg fresh Arnica Flowers)

Extractant: ethanol 58 %v/v

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gel.

It is a clear golden-brown to green yellow coloured gel with a characteristic odour of Arnica.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

A traditional herbal medicinal product for the symptomatic relief of muscular aches, pains and stiffness, sprains, bruises and swelling after contusions, exclusively based on long-standing use.

4.2 Posology and method of administration

Adults: Apply 2 - 10 cm gently to the affected area 2 to 4 times daily.

Children and the elderly: Apply similarly as described for adults (above).

For cutaneous use only.

4.3 Contraindications

Do not use in cases of known hypersensitivity to Arnica preparations, other members of the Asteraceae (Compositae) family, or one of the excipients.

4.4 Special warnings and precautions for use

Do not exceed the stated dose.

If the condition worsens, or if symptoms persist for more than two weeks, or if adverse events not mentioned in the package leaflet occur, consult a healthcare

practitioner.

For cutaneous use only. Do not use on broken or irritated skin. Avoid contact with eyes and mucous membranes. Discontinue use if redness, irritation or dry skin occurs.

Keep out of the sight and reach of children.

4.5 Interaction with other medicinal products and other forms of interaction

None known.

4.6 Pregnancy and lactation

Pregnancy: There is no evidence of the safety of the product in human pregnancy, nor is there any evidence from animal studies. Although no adverse reactions have been observed, the use of the product during pregnancy should be avoided unless under the guidance of a medical practitioner.

Lactation: There is no evidence to suggest that the product should not be used during lactation.

4.7 Effects on ability to drive and use machines

Atrogel has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Common ($>1/100$ to $\leq 1/10$)
Skin and subcutaneous tissue disorders.

Contact dermatitis
Itching
Rash
Dry Skin

The incidence is reported in studies to be between 5 and 10% for Atrogel.

4.9 Overdose

In case of overdose, irritation and redness may occur. Discontinue use.

In the unlikely event of internal ingestion, due to the irritant effect of Arnica, symptoms of intoxication may include gastro-intestinal and nervous system disturbances; dizziness, diarrhoea, shivering and palpitations. Respiratory difficulties may occur at very high doses. Treatment of overdose: the stomach should be emptied by aspiration or lavage if the patient has not already vomited. Demulcent drinks such as milk should be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Not applicable.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol (96 %)
Purified water
Glycerol (85 %)
Hypromellose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Pack: White laminated multilayer polyethylene tube with a vapour block layer (SiO_x-layer). The opening is sealed with an aluminium peel-seal.

Closure: Polypropylene screw cap.

Pack size: 100 ml

6.6.1 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product.

No special requirements

7 REGISTRATION HOLDER

Bioforce (UK) Ltd
2 Brewster Place
Irvine, Ayrshire
KA11 5DD, United Kingdom
Tel: 01294 277 344
enquiries@avogel.co.uk

8 REGISTRATION NUMBER(S)

THR 13668/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/10/2006

10 DATE OF REVISION OF THE TEXT

30/10/2006

PATIENT INFORMATION LEAFLET



Package Leaflet:
Information for the User

A.Vogel

Atrogel
Arnica Gel



Information

Read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription. However, you still need to use Atrogel carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- If you need more information or advice ask your doctor, pharmacist or healthcare practitioner.
- You must contact a doctor, pharmacist or healthcare practitioner if your symptoms worsen or do not improve within 2 weeks.
- If any of the side effects become serious, or if you notice any side effect not listed in this leaflet, please tell your doctor, pharmacist or healthcare practitioner.

In this leaflet:

1. What Atrogel is and what it is used for
2. Before you use Atrogel
3. How to use Atrogel
4. Possible side effects
5. How to store Atrogel
6. Further information



Do's and Don'ts for using Atrogel

1. What Atrogel is and what it is used for

Atrogel is a traditional herbal medicinal product for relieving muscular aches and pains based exclusively on long-standing use.

Used to help relieve symptoms including:

- Muscular aches, pains and stiffness
- Sprains
- Bruises
- Swelling after injury

2. Before you use Atrogel

Do not use Atrogel if you are allergic to:

- Arnica Flower extract
- Any other ingredients of Atrogel (see Section 6 Further Information)
- Any products containing Arnica
- Any products containing members of the daisy (Asteraceae/Compositae) family. Arnica is a member of the daisy family.

Take special care with Atrogel

- Don't use at more than the recommended dose.
- Don't use in or near your eyes, nose, mouth or other sensitive areas. It may cause irritation.
- Don't use on broken, cut or irritated skin. It may cause irritation.
- If your symptoms worsen see your doctor, pharmacist or healthcare practitioner.
- If you do not feel any benefit from it within two weeks see your doctor, pharmacist or healthcare practitioner.

Using other medicines

- You can use Atrogel with other medicines.

Using Atrogel with food and drink

- You can eat and drink as normal whilst using Atrogel.

Pregnancy and breast-feeding

- If you are pregnant speak to your doctor, pharmacist or healthcare practitioner before use.
- Atrogel is suitable for use if you are breast-feeding.

Driving and using machines

- Atrogel has no effect on your ability to drive or use machines.

Please turn over...

Using

3. How to use Atrogel

Adults: Apply 2 - 10 cm gently to the affected area. Use 2 to 4 times a day.

Children and the elderly: Follow the adult dose.

For external use only. This means you can use Atrogel on your skin but not in or near your eyes, nose, mouth or other sensitive areas. Do not apply if your skin surface is broken, cut or irritated.

When first opening the tube check that the seal is not broken. Remove seal before use.

If you use more Atrogel than you should

- Your skin may become red or irritated. If this happens stop using Atrogel.

If you forget to use Atrogel

- Don't worry. Continue to use as before.

If you stop using Atrogel

- You can stop using Atrogel at any time.

If you feel Atrogel isn't working

- Contact a doctor, pharmacist or healthcare practitioner if your symptoms worsen or do not improve within 2 weeks.

There is additional information in Section 6 at the end of this leaflet.

Side effects

4. Possible side effects

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

Minor effects

The following minor effects can occur when using Atrogel.

These are likely to affect less than 1 in every 10 people.

- Itching
- Rash
- Skin reaction (contact dermatitis)
- Dry skin

Discontinue use. If you find these are troubling you, talk to a doctor, pharmacist or healthcare practitioner.

If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, pharmacist or healthcare practitioner.

If Atrogel is swallowed by mistake

- Contact your doctor, pharmacist or healthcare practitioner immediately.

Information

5. How to store Atrogel

- Replace cap after use.
- Keep out of the reach and sight of children.
- Do not use Atrogel after the expiry date which is stated on the carton and tube.
- This medicinal product does not require any special storage conditions.
- Do not use Atrogel if you notice a change in colour. It is a clear gel which should appear golden-brown to yellowy-green in colour.

6. Further Information

What Atrogel contains

The active ingredient is the liquid extract of fresh Arnica flowers. 1 g of gel contains 500 mg of extract which is equivalent to an average of 160 mg fresh Arnica flowers.

The other ingredients are ethanol, purified water, glycerol (plant origin), hypromellose (thickener).

What Atrogel looks like and the contents of the pack

Atrogel is a clear gel which should appear golden-brown to yellowy-green in colour. It is available in a 100 ml tube.

Traditional Herbal Registration Holder/Manufacturer

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

THR No. 13668/0009

This leaflet was approved on 10/2006

You should also know

Don't use too much Atrogel as this may stain your clothes.

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

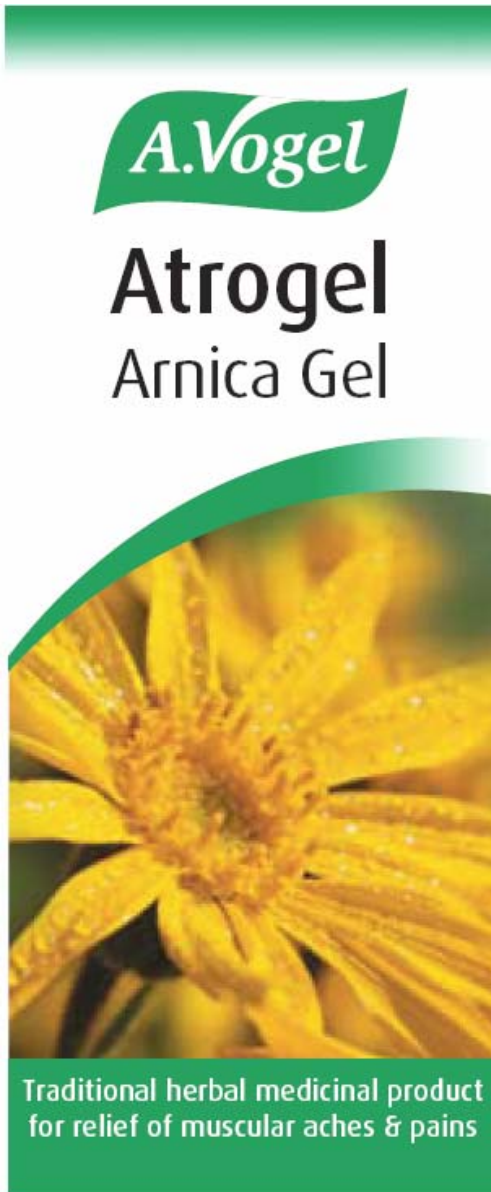
Email: enquiries@avogel.co.uk

Phone: 0845 608 5858

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

Call this number:
0845 608 5858.

LABELLING



The image shows the front of a white tube of A. Vogel Arnica Gel. At the top, the A. Vogel logo is displayed in white text on a green leaf-shaped background. Below the logo, the product name 'Atrogel Arnica Gel' is printed in a large, bold, black font. A curved green band at the bottom of the tube contains the text 'Traditional herbal medicinal product for relief of muscular aches & pains' in white. The central part of the tube features a close-up photograph of a bright yellow Arnica flower with green leaves.

Atrogel is a traditional herbal medicinal product for relieving muscular aches and pains based exclusively on long-standing use. Used to help relieve symptoms including:

- Muscular aches, pains and stiffness
- Sprains
- Bruises
- Swelling after injury

Directions for use:
Before first use check that the tube seal is not broken. Remove tube seal before use.

Adults: Apply 2 – 10 cm gently to the affected area. Use 2 to 4 times a day.

Children and the elderly: Follow the adult dose. For external use only. Read leaflet before use. Consult a doctor, pharmacist or healthcare practitioner if symptoms persist or adverse effects not mentioned in the package leaflet occur.

Do not use in or near eyes, nose, mouth and other sensitive areas.

Do not use on broken, cut or irritated skin.

Do not use if you are allergic to Arnica preparations, other members of the daisy (Asteraceae/Compositae) family or any of the other ingredients. Keep out of the reach and sight of children.

LOT/EXP: See end of tube

Ingredients: The active ingredient is the liquid extract of fresh Arnica flowers. 1 g of gel contains 500 mg of extract which is equivalent to an average of 160 mg fresh Arnica flowers. The other ingredients are ethanol, purified water, glycerol (plant origin) and hypromellose (thickener).

Traditional Herbal Registration Holder/Manufacturer:
Bioforce (UK) Ltd, Irvine KA11 5DD
THR No. 13668/0009 100 ml e

Extract of fresh Arnica flowers

90397.02/081106

2020012



100 ml e

Atrogel
Arnica Gel
A.Vogel

A.Vogel

A.Vogel

Atrogel
Arnica Gel

A.Vogel

Atrogel
Arnica Gel

A.Vogel

Atrogel
Arnica Gel

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Do not use if you are allergic to Arnica preparations, other members of the daisy (Asteraceae/Compositae) family or any of the other ingredients.

Keep out of the reach and sight of children.

Traditional Herbal Registration Holder/
Manufacturer:
Bioforce (UK) Ltd,
Irvine, Ayrshire KA11 5DD
Telephone: 01294 277344

THR No. 13668/0009

2020002

Extract of fresh Arnica flowers

100 ml e

Traditional herbal medicinal product for relief of muscular aches & pains

100 ml e



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