# Natures Aid Milk Thistle tablets

**THR 33336/0005**

**UKPAR**

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Natures Aid Ltd a Traditional Herbal Registration Certificate for the traditional herbal medicinal product Natures Aid Milk Thistle tablets (Traditional Herbal Registration number: THR 33336/0005) on 15 March 2012. This product is available without prescription and can be bought from pharmacies and other outlets.

Natures Aid Milk Thistle tablets are traditional herbal medicinal products used to relieve the symptoms associated with occasional over indulgence of food and drink such as indigestion and upset stomach, based on traditional use only. The active ingredient of Natures Aid Milk Thistle tablets comes from the fruit of the Milk thistle plant (Silybum marianum (L.) Gaertner).

This registration is based exclusively upon the longstanding use of Milk thistle fruit 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 a 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.
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SCIENTIFIC DISCUSSION

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The MHRA granted a Traditional Herbal Registration Certificate for the traditional herbal medicinal product Natures Aid Milk Thistle tablets (THR 33336/0005) to Natures Aid Ltd on 15 March 2012. 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. Natures Aid Milk Thistle tablets are used to relieve the symptoms associated with occasional over indulgence of food and drink, such as indigestion and upset stomach, based on traditional use only.

The data supplied by the applicant demonstrate 30 years of traditional use of Milk thistle fruit in the EU. A satisfactory review of the available safety data on Milk thistle fruit has also been provided, together with an Expert Safety Report supporting the proposed product.
PHARMACEUTICAL ASSESSMENT

HERBAL SUBSTANCE: MILK THISTLE FRUIT
Latin name of plant: Silybum marianum (L.) Gaertner
Common name of plant: Milk thistle
Plant family: Asteraceae

The Milk thistle plants used in this product are grown in the Europe. The fruits are harvested during July and August.

Confirmation has been provided that the herbal substance is produced in line with the Guideline on Good Agricultural and Collection Practice (GACP) EMEA/HMPC/246816/2005 and that the herbal substance has not been fumigated or treated with ionizing radiation during growing or storage.

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.

Container Closure System
Satisfactory details of the container closure system are provided and confirmation has been given that all components of the container closure system comply with current legislation relating to plastic materials and articles intended to come into contact with foodstuffs.

Stability
Satisfactory stability studies have been carried out on the Milk thistle fruit.

HERBAL PREPARATION: MILK THISTLE FRUIT DRY EXTRACT
Drug extract ratio (DER): 20-40:1
Extraction solvent: Ethyl acetate 100 % v/v

Manufacture
A satisfactory description of the manufacturing process of the herbal preparation and flow diagram has been provided. The in-process controls are satisfactorily detailed. 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.

**Container Closure System**
Confirmation is provided that all components of the container closure system used to store this herbal preparation comply with current legislation relating to plastic materials and articles intended to come into contact with foodstuffs.

**Stability**
Stability studies have been performed in accordance with current guidelines. The proposed re-test period for the Milk thistle dry extract is acceptable.

**HERBAL PRODUCT: NATURES AID MILK THISTLE TABLETS**

**Description and Composition of the Herbal Product**
Natures Aid Milk Thistle tablets are yellow–yellow/brown, oval, bi-convex uncoated tablets. Each tablet contains 137.5 mg–165 mg of standardised dry extract from Milk thistle fruit. The rest of the tablet is composed of calcium hydrogen phosphate anhydrous, cellulose microcrystalline, silica colloidal hydrated, croscarmellose sodium and magnesium stearate.

The compatibility of the herbal preparation with the excipients is demonstrated by the stability testing results. The excipients are controlled in line with their respective Ph Eur monograph. The magnesium stearate used in the product is confirmed to be of vegetable origin. Certificates of Analysis have been provided for all excipients.

**Manufacture**
A flow diagram outlining the various stages of the manufacturing process and the in-process controls is provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Currently, process validation has not been carried out on commercial batches, however, as the manufacturer has committed to carry out process validation on commercial batches following an appropriate process validation protocol, this is acceptable.

**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.

**Container Closure System**
The tablets are stored in Ph Eur type III glass bottles with polypropylene cap incorporating an induction heat seal liner. The bottles are inserted into a printed outer carton containing a Patient Information Leaflet. The approved pack sizes are for 30, 60, 90 or 120 tablets, although not all pack sizes may be marketed.
Suitable specifications have been provided by the packaging suppliers and it has been confirmed that all primary packaging materials comply with current legislation relating to plastic materials and articles intended to come into contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a product shelf-life of 2 years is appropriate when the storage precautions ‘Store below 25°C’ and ‘Store in the original package’ are applied.

**Pharmaceutical Expert**

The Quality Overall Summary has been written by a suitably experienced expert.

**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.

**CONCLUSION**

There are no objections to granting of a Traditional Herbal Registration Certificate from a quality point of view.
NON-CLINICAL ASSESSMENT

NON-CLINICAL OVERVIEW
An Expert Safety Report was provided, which included reviews of some non-clinical data. The Expert Safety Report was written by a suitably qualified professional.

Due to a shortage of published data on Milk thistle fruit it is not possible to assess if the safety package for the phytochemical constituents of Milk thistle fruit 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 may be acceptable and in compliance with guideline EMEA/HMPC/32116/05.

Following genotoxicity testing Milk thistle extract was found to be mutagenic in the TA98 strain (but not the TA100, TA1535, TA1537 and TA102 strains) of *S typhimurium*. It was also considered to be mutagenic in a mammalian chromosomal aberration assay at the maximum concentration evaluated (240 mcg/mL). However, it was not mutagenic in an in vivo chromosomal aberration assay at a dose that was substantially (47-fold) higher than the maximum proposed clinical dose of 522 mg or 10.4 mg/kg/day. In addition, no indication of carcinogenic potential was observed during two-year studies in the mouse or rat, following repeated oral administration of up to 7180 or 2750 mg/kg/day, respectively.

The overview submitted in support of this application is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The SmPC for this product is satisfactory from a non-clinical 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
There are no objections to granting of a Traditional Herbal Registration Certificate from a non-clinical point of view.
CLINICAL ASSESSMENT

INDICATION
The applicant has proposed the following therapeutic indication:

‘A traditional herbal medicinal product used to relieve the symptoms associated with occasional over indulgence of food and drink such as indigestion and upset stomach based on traditional use only.’

The indication is acceptable.

POSOLOGY AND METHOD OF ADMINISTRATION
The applicant proposed the following:

“For oral use only.
Adults and the elderly: take 1 – 2 tablets twice daily. Swallow the tablet(s) whole with some liquid.
This product is not recommended for use in children or adolescents under 18 years of age (See Section 4.4. Special warnings and precautions for use)
If the condition worsens, or symptoms persist, a doctor or qualified healthcare practitioner should be consulted.”

This is acceptable.

EFFICACY
No clinical efficacy data is required for registration of Traditional Herbal Medicinal Products.

EVIDENCE OF TRADITIONAL 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 EU.

The applicant has provided a bibliographic review as evidence of the use of Milk thistle fruit within the EU for a period exceeding 30 years.

The information provided is considered to satisfy the requirement to demonstrate use for at least 30 years, of which at least 15 years have been in an EU Member State. The requirements of the Directive are, therefore, addressed for this aspect.

SAFETY REVIEW
Article 16 c 1 (d) requires the applicant to provide a bibliography of the safety data together with an Expert Safety Report.

A safety review has been provided as well as an Expert Safety Report written by a suitably qualified professional. These are satisfactory.
PRODUCT LITERATURE
The SmPC, PIL and labelling for this product are medically satisfactory.

CONCLUSION
There are no objections to granting of a Traditional Herbal Registration Certificate from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT: RISK ASSESSMENT

QUALITY
The quality data submitted with this application are satisfactory.

NON-CLINICAL
The results of genotoxicity testing are provided with this application and are satisfactory.

EFFICACY AND SAFETY
No clinical efficacy data are required for registration of Traditional Herbal Medicinal Products. The applicant has provided a bibliographic review which shows ample evidence for the use of Milk thistle fruit within the EU for a period exceeding 30 years.

A satisfactory review of the safety data has also been provided.

The SmPC, PIL and labelling are satisfactory.

BENEFIT: RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The benefit: risk balance is acceptable and a Traditional Herbal Registration Certificate may be granted.
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STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Traditional Herbal Registration application on 17 September 2010
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 30 September 2010
3. Following assessment of the application the MHRA requested further information relating to the clinical dossier on 17 March 2011
4. The applicant responded to the MHRA’s request, providing further information on the clinical dossier on 12 April 2011
5. Following assessment of the response the MHRA requested further information relating to the clinical dossier on 24 May 2011 and the quality dossier on 2 June 2011
6. The applicant responded to the MHRA’s request, providing further information on the quality dossier on 16 September 2011
7. Following assessment of the response the MHRA requested further information relating to the quality dossier on 26 September 2011
8. The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 9 March 2012 and the clinical dossier on 12 March 2012
9. A THR was granted on 15 March 2012
1 NAME OF THE MEDICINAL PRODUCT
Natures Aid Milk Thistle tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 137.5mg – 165mg of standardised extract (as dry extract) from Milk Thistle fruits (*Silibum marianum* (L) Gaertner), (equivalent to between 2750mg and 6600mg of Milk Thistle fruits) corresponding to 82.5mg Silymarin calculated as Silibinin.

Extraction solvent: ethyl acetate 100% v/v.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablets
A yellow – yellow/brown oval bi-convex uncoated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
A traditional herbal medicinal product used to relieve the symptoms associated with occasional over indulgence of food and drink such as indigestion and upset stomach based on traditional use only.

4.2 Posology and method of administration
For oral use only.
Adults and the elderly: take 1 – 2 tablets twice daily. Swallow the tablet(s) whole with some liquid.
This product is not recommended for use in children or adolescents under 18 years of age (See Section 4.4. Special warnings and precautions for use)
If the condition worsens, or symptoms persist, a doctor or qualified healthcare practitioner should be consulted.

4.3 Contraindications
Hypersensitivity to the active substance or other members of the Asteraceae /Compositae family or any of the excipients

4.4 Special warnings and precautions for use
Do not exceed the stated dose.
The use of this product in children and adolescents under 18 years of age is not recommended as there is no relevant indication.
Patients suffering from active liver disease should consult their doctor before taking this product.
Milk Thistle may alter the way certain drugs are broken down by the liver (see Section 4.5 ‘Interaction with other medicinal products and other forms of interaction’)

4.5 Interaction with other medicinal products and other forms of interaction

*In vitro*, Milk Thistle extract resulted in inhibition of CYP isoenzymes. However, the clinical relevance of these findings is not established.

4.6 Fertility, pregnancy and lactation

The safety of the product during pregnancy has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.
Animal studies are insufficient with respect to reproductive toxicity (see Section 5.3)

Studies on the effects of fertility have not been performed.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Gastrointestinal reactions (nausea, upset stomach, diarrhoea), headache, allergic reactions (urticaria, skin rash, pruritis, anaphylaxis).
The frequency is not known.
If other adverse reactions not mentioned above occur, a doctor or qualified healthcare practitioner should be consulted.

4.9 Overdose

No case of overdose has been reported.
Supportive and symptomatic treatment should be provided as appropriate.

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

In the mouse, the acute oral toxicity of silymarin in milk thistle extracts was found to be in excess of 2000mg/kg. No deaths occurred within 48 hours of administration. In the rat, repeated oral administration of 1000 mg/kg/day for 15 days or 100mg/kg for 16 or 22 weeks showed no adverse effects when compared with controls. In a separate study, repeated oral administration of 1050, 2180, or 4500 mg/kg/day caused reductions in sperm motility and the number of spermatid heads per testis by up to 11% and 21% respectively. However, the observed effects were not associated with any histopathological
findings and were not evident in mice following repeated oral administration of up to 11620 mg/kg for 3 months. Following repeated oral administration of silymarin to pregnant rats (at 1000 mg/kg/day from day 8 to day 12 of gestation) and rabbits (at 100mg/kg from day 8 to day 17), no embryotoxic effects were evident on day 21 of pregnancy. Milk Thistle extract was considered to be mutagenic in the TA98 strain (but not the TA100, TA1535, TA1537 and TA102 strains) of *S typhimurium*. It was also considered to be mutagenic in a mammalian chromosomal aberration assay at the maximum concentration evaluated (240 mcg/mL). However, it was not mutagenic in an in vivo chromosomal aberration assay at a dose that was substantially (47-fold) higher than the maximum proposed clinical dose of 522 mg or 10.4 mg/kg/day. In addition, no indication of carcinogenic potential was observed during two-year studies in the mouse or rat following repeated oral administration of up to 7180 or 2750 mg/kg/day, respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Calcium hydrogen phosphate anhydrous
Cellulose microcrystalline
Silica colloidal hydrated
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C. Store in the original package

6.5 Nature and contents of container
Ph Eur type III glass bottles with polypropylene cap incorporating an induction heat seal liner. Printed outer carton containing Patient Information Leaflet.
Pack sizes: 30, 60, 90, 120 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Natures Aid Ltd
St Georges Park
Kirkham
Preston
Lancashire PR4 2DQ
Tel: 01772 686231
Fax: 01772 671688
email: sales@naturesaid.co.uk

8 MARKETING AUTHORISATION NUMBER(S)
THR 33336/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/03/2012

10 DATE OF REVISION OF THE TEXT
15/03/2012
PATIENT INFORMATION LEAFLET

Milk Thistle tablets
Milk Thistle standardised fruit extract

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 this product carefully
to get the best results from it.
Keep this leaflet. You may need to read it again.
Ask your doctor, pharmacist, or qualified healthcare practitioner if you need more information or advice.
You must consult a doctor or qualified healthcare practitioner if symptoms worsen or do not improve
after 1 week.
If any side effect gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. What the product is and what it is used for
2. Before you take this product
3. How to take this product
4. Possible side effects
5. How to store this product
6. Further information

1. WHAT THE PRODUCT IS AND WHAT IT IS USED FOR

This is a traditional herbal medicinal product containing Milk Thistle standardised fruit extract used
for the relief of symptoms associated with occasional over indulgence of food and drink such as
indigestion and upset stomach based on traditional use only.
Each tablet contains 137.5mg - 185mg of standardised extract (as dry extract) from Milk Thistle
fruits (Silibum marianum (L) Gaertner). (Equivalent to 2750mg - 6600mg of Milk Thistle fruit)
corresponding to 82.5 mg of silymarin, calculated as silibinin.
Extraction solvent: ethyl acetate 100% v/v.

2. BEFORE YOU TAKE THIS PRODUCT

This product is not suitable for patients under 18 years of age.

Do not take this product if:
• You are allergic to Milk Thistle, any other members of the Asteraceae/Compositae family such as
marigolds, daisies or artichokes, or any of the other ingredients (see section 6 for more information).

Take special care with this product:
• Tell your doctor before taking this product if you are currently suffering from any liver disorders.

Taking other medicines.
If you are taking other medicines, tell your doctor or pharmacist before taking this medicine.
Pregnancy and breastfeeding.
Do not take this product if you are pregnant of breastfeeding, because there is no evidence that
it is safe to do so.
3. **HOW TO TAKE THIS PRODUCT**

For oral use only. Adults and the elderly: Swallow one to two tablets twice daily. Swallow the tablet whole with some liquid.

Do not take if you are under 18 years of age.

Do not exceed the recommended dose.

After using this product

If your symptoms worsen or do not improve after one week, consult your doctor or qualified healthcare practitioner.

If you take too much of this product (overdose)

If you have taken more than you should and feel unwell, talk to your doctor or qualified healthcare practitioner as soon as possible.

If you forget to take this product

Do not take a double dose to make up for a forgotten dose. Take the next dose when it becomes due.

If you have any questions or are not sure how to use this product, consult your doctor or qualified healthcare practitioner.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, this product can cause side effects, although not everybody gets them. The frequency of effects is not known. Possible side effects include:

- Mild allergic skin reactions such as itching and/or skin rash, urticaria, hives, pruritus or anaphylaxis.

- If you experience an allergic reaction, stop taking this product.

- Other side effects that may occur are feeling sick, diarrhoea, upset stomach and headache.

- If any of the effects become troublesome or if you experience any other side effects, consult your doctor or pharmacist.

5. **HOW TO STORE THIS PRODUCT**

Keep out of the reach and sight of children.

Do not store above 25°C. Store in original package.

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

Do not use this product if you notice any discolouring or softening of the tablets, as this means they may have deteriorated.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. **FURTHER INFORMATION**

One tablet contains 137.5mg - 165mg of standardized extract (as dry extract) from Milk Thistle fruits (*Silibum marianum* (L) Gaertner), (equivalent to 2750mg - 6600mg of Milk Thistle fruit.) corresponding to 82.5mg of silymarin, calculated as silybin.

It also contains other ingredients: calcium hydrogen phosphate anhydrous; cellulose microcrystalline; silica colloidal hydrated; croscarmellose sodium; magnesium stearate.

The product is available in packs of 30, 60, 90 and 120 tablets (not all sizes may be marketed).

Registration number: THR 33336/0005

Traditional Herbal Registration Holder and Manufacturer:

Natures Aid Ltd, St Georges Park, Preston, Lancs. PR4 2DQ

Tel: 01772 686231; Fax: 01772 671688; e-mail: sales@naturesaid.co.uk

You can also help to make medicines safer by reporting any side-effects to the Yellow Card Scheme at www.mhra.gov.uk/yellowcard. Alternatively, you can get a paper Yellow Card form from your GP's surgery or pharmacy, or call free phone 0808 100 3352 (available 10am – 2pm Monday – Friday). This leaflet was last revised 03/2012.

For a large print, braille or audio version of this leaflet please call 01772 686231
Label:

Milk Thistle

Active Ingredients:
One tablet contains 137.5mg - 165mg of standardised extract (as dry extract) from Milk Thistle (Silybum marianum L.) fruit, equivalent to 275mg and 330mg of Milk Thistle fruit, corresponding to 82 mg thymoquinin calculated as 580mg.

Extraction Solvent:
Glycol/methanol 10:1 v/v.
Registration holder/manufacturer:
Natures Aid Ltd.

60 Tablets

DO NOT USE IF SEAL IS BROKEN

NATURES AID LTD, PRESTON, PR1 2DH, UK.

MHRA PAR; NATURES AID MILK THISTLE TABLETS, THR 33336/0005
Carton: