Public Assessment Report

CBG MEB

Diao Xin Xue Kang, capsules for oral use
SU BioMedicine B.V., The Netherlands

RVG 102142

NL-PAR
TRADITIONAL HERBAL MEDICINAL PRODUCT

Route of administration:	oral
Prescription status:	non-prescription, uitsluitend apotheek of drogist (UAD)
Therapeutic indication:	Traditioneel kruidengeneesmiddel toegepast ter verlichting van hoofdpijn en bij spierpijn en spierkrampen in nek, rug en benen. De toepassing is uitsluitend gebaseerd op traditioneel gebruik en niet op klinisch bewijs.
Date of authorisation in NL:	14 March 2012
Application type/legal basis:	Directive 2001/83 article 16a

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I LAY SUMMARY

The Medicines Evaluation Board (MEB) has granted SU BioMedicine B.V. from the Netherlands a registration for Diao Xin Xue Kang, capsules for oral use as a Traditional Herbal Medicinal Product (Registration number: RVG 102142). This product is available without prescription. The sale is restricted to pharmacies and drugstores.

Diao Xin Xue Kang capsules, contain 100 mg of a dried water extract of the dried rhizomes of *Dioscorea nipponica* Makino., equivalent to 5-6.67 g of dried plant material. The drug to extract ratio is 50.0-66.7:1. Diao Xin Xue Kang is used as a "*Traditioneel kruidengeneesmiddel toegepast ter verlichting van hoofdpijn en bij spierpijn en spierkrampen in nek, rug en benen. De toepassing is uitsluitend gebaseerd op traditioneel gebruik en niet op klinisch bewijs."* (Traditional medicinal product for the relief of headache and muscular pains and muscle cramps in the neck, back and legs. This use is based on traditional use only and not on demonstrated clinical efficacy).

The registration of Diao Xin Xue Kang capsules, is based exclusively upon the longstanding use of *Dioscorea nipponica* root as a traditional herbal medicinal product in both China and Europe 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.

The three most important areas of assessment (traditional use, quality and safety) are satisfactory and it was therefore decided that a registration as Traditional Herbal Medicinal product could be granted.

Legal background: What are Traditional herbal medicinal products?
Some plants contain substances that may be used to treat diseases. Medicinal products that are prepared from plants are known as "herbal medicinal products". Even though they are "natural", a number of these products may be potentially dangerous for patients. This is why herbal medicinal products are covered by pharmaceutical legislation, with aims to protect public health by ensuring the safety, efficacy and quality of medicinal products.
Within the group of herbal medicinal products, some have a long tradition of use. European Union (EU) legislation classifies as *traditional herbal medicinal products* those herbal medicinal products that have been used for at least 30 years, including at least 15 years within the EU, are intended to be used without the supervision of a medical practioner (in NL normally classified as UAD) and are not administered by injection.

Why did the EU decide to adopt specific legislation on traditional herbal medicinal products?
All medicinal products, including herbal medicinal products, need a marketing authorisation to be placed on the EU market. Traditional herbal medicinal products have particular characteristics, notably their long tradition of use. To take account of this, the EU introduced a lighter, simpler and less costly registration procedure for them, while providing the necessary guarantees of quality, safety and efficacy.
The Herbal Directive (Directive 2004/24/EC) was adopted to facilitate the placing on the EU market of traditional herbal medicinal products. This simplified procedure allows the registration of traditional herbal medicinal products without requiring safety tests and clinical trials, which the applicant is obliged to provide under the full marketing authorisation procedure.
The long tradition of the herbal medicinal product makes it possible to reduce the need for these tests and trials that can be replaced by documentation which indicates that the product is not harmful in specified conditions of use and that its efficacy is plausible on the basis of long-standing use and experience. However, occasionally even a long tradition of use does not exclude concerns about the product's safety. In such cases competent authorities of the Member States are entitled to ask for additional data, if they deem it necessary to assess the safety of the traditional herbal medicinal product.

Does the Herbal Directive impose new requirements for the placing on the market of traditional herbal medicinal products?
Before 2004, herbal medicinal products were covered by the same requirements as other medicinal products. The Herbal Directive amends those requirements and provides for a simplified registration procedure introduced to facilitate the placing on the market of traditional herbal medicinal products. This simplified procedure allows

registration of traditional herbal medicinal products based on sufficient evidence of medicinal use throughout a period of at least 30 years, including at least 15 years in the European Union.
The long tradition of the herbal medicinal product makes it possible to reduce the need for clinical trials, in so far the pharmacological effects or efficacy are plausible on the basis of long-standing use and experience. Non-clinical tests are considered unnecessary, where the herbal medicinal product on the basis of its traditional use proves not to be harmful in specified conditions of use.
The quality of the herbal medicinal product is independent of its traditional use so no derogation is made with regard to the regular quality requirements. Traditional herbal medicinal products should comply with quality standards in the European Pharmacopoeia.

II SCIENTIFIC DATA

II.1 Introduction

This application was submitted according to Article 16a of Directive 2001/83 EC, as amended.

The MEB granted a registration as traditional herbal medicinal product for Diao Xin Xue Kang capsules, from SU Biomedicine BV, the Netherlands. The manufacturer is D'iao Pharmaceuticals, Chengdu, China. This product is classified as UAD (Uitsluitend Apotheek en Drogist), which means that sale is restricted to only pharmacies or drugstores.

Diao Xin Xue Kang consists of capsules with100 mg of a dried water extract (Drug to extract ratio: 50.0-66.7:1) of the dried rhizomes of *Dioscorea nipponica* Makino as active ingredient. The product is authorized with the indication: "*Traditioneel kruidengeneesmiddel toegepast ter verlichting van hoofdpijn en bij spierpijn en spierkrampen in nek, rug en benen. De toepassing is uitsluitend gebaseerd op traditioneel gebruik en niet op klinisch bewijs".* (Traditional medicinal product for the relief of headache and muscular pains and muscle cramps in the neck, back and legs. This use is based on traditional use only and not on demonstrated clinical efficacy).

The data supplied by the Marketing Authroization Holder (MAH) substantiates 30 years of medicinal use of *Dioscorea nipponica* Makino, including at least 15 years in the European Community. A satisfactory review of the available safety data of *Dioscorea nipponica* Makino has also been provided, together with Expert Safety Reports supporting the safety of Diao Xin Xue Kang capsules.

At the time of assessment and registration a Community Herbal Monograph of *Dioscorea nipponica* Makino was not yet established.

At the time of assessment there were no preparations of *Dioscorea nipponica* Makino registered as medicinal product in the European Union but in China and Russia extracts of *Dioscorea nipponica* Makino were on the market for more than 30 years.

Community Monographs/ -List Entries:

What is the role of the Community Herbal Monographs and Community List Entries, as established by the Herbal Medicinal Products Committee (HMPC), at the European Medicines Agency in London?
The European Medicines Agency does not have a role in the registration of traditional herbal medicinal products in a Member State. The simplified procedure is a national one. This means that applications for registration as traditional herbal medicinal product needs to be submitted in each Member State where the product is to be marketed. These applications are evaluated by the competent authority in each Member State. (in the Netherlands: Medicines Evaluation Board).
The Herbal Medicinal Products Committee in London has the task to prepare a Community List of traditional herbal substances and –preparations, as well as establish Community Herbal Monographs for traditional herbal medicinal products. Where a Community List entry is established, this shall be recognized by competent authorities as a basis for registration.

When new Community herbal monographs will be established, the registration holder shall consider whether it is necessary to modify the registration dossier accordingly.

II.2 QUALITY

II.2.1 HERBAL SUBSTANCE

General information

Latin name:	*Dioscorea nipponica Makino* L.
Family:	Dioscoreaceae
Parts of plant used:	Rhizomes (dried)
Origin:	Henan Province, People's Republic of China

Manufacture

The starting material is cultivated in the Henan Province of the People's Republic of China. The cultivation of the plant and collection of the plant material are in accordance with the guideline on Good Agricultural and Collection practise (EMEA/HMPC/24618/2005). Environmental monitoring is performed on the air, soil and irrigation water of the cultivation location. The cultivation period of *Dioscorea nipponica* Makino is three years. The MAH has provided a satisfactory description of cultivation and harvesting including information on rhizome selection, planting, fertilizers used, time-, method and amount of fertilization, weeding, as well a list of pesticides used. The use of fertilizers and pesticides is recorded in detail.

Roots are harvested 3 years after planting, at the end of November. After harvesting the herbal material is washed with tap water in a drum-type herbal washing machine. Satisfactory specifications and a certificate of analysis of the tap water were provided. The material is cut into slices in a rotary slicing machine and then dried in circulating hot air oven (electrical heating). No fumigants are used during the manufacturing process.

After removal of the rootlets and outer bark the herbal substance is packed and stored for a maximum of two years.

Control of herbal substance

Release specifications of the herbal substance are satisfactory and comprise of general characteristics, identification by microscope and TLC, foreign matter, residual solvent, microbiologicall quality, toxic metals, radioactivity, pesticides and marker content.

Analytical methods have been appropriately validated and are adequate for ensuring compliance with the relevant specifications. All specifications are supported by the batch data provided.

Reference Standards or Materials

Satisfactory characterization of the primary and working reference standards have been provided.

Stability

Stability studies have been conducted with three production scale batches in the final container closure system. Batches were tested in accordance with the release specification using the same test methods. The data support the storage conditions and shelf life. All parameters tested remained within specifications under all conditions tested.

II.2.2 HERBAL PREPARATION

General information

Herbal preparation:	Dry extract of the rhizomes of *Dioscorea nipponica* Makino
Scientific name of the plant:	*Dioscorea nipponica*
Parts of the plant used:	Rhizomes
Extraction solvent:	Purified water (Ph. Eur.)
Drug Extract Ratio (DER):	50.0-66.7:1

Manufacture

The herbal preparation is produced under GMP (Good Manufacturing Practice) conditions. Manufacturing practices were inspected and approved by the Dutch Inspectorate (IGZ) in November 2009 and re-inspected in June 2012. GMP certificates can be found on http://eudragmp.ema.europa.eu

A satisfactory, detailed description of the manufacturing process (extraction, drying, blending), including batch size, manufacturing formula, process conditions, in process controls and flow diagram, has been provided.
The in-process controls and specifications are sufficiently detailed, and justified.

Control of the herbal preparation

Suitable tests are performed to elucidate the structure and other characteristics of the herbal preparation. Release specifications for the extract comprise of appearance, identification by TLC fingerprint, marker content, loss on drying, residual solvent, pesticides, heavy metals, aflatoxins and microbiological purity. Identity is tested in accordance with the monograph of the Chinese pharmacopoeia. Loss on drying, acid-insoluble ash, heavy metals, aflatoxins, and pesticides are tested in accordance with Ph. Eur.
Residual solvents and radioactive contamination were tested with adequately validated analytical methods. Specifications are in accordance with Ph. Eur. requirements where appropriate or otherwise justified. Certificates of analysis of three batches of extract were presented. All data comply with the proposed specifications.

Reference Standards or Materials

Satisfactory characterization of the primary reference standards have been provided.

Container closure system

The herbal preparation is stored in a suitable container closure system. A description of the container closure system and its specifications are provided. The stability data provided show no incompatibilities between the herbal preparation and the container. Confirmation is provided that the components of the containers are in compliance with EU Directives relating to plastic materials and articles intended to come into contact with foodstuffs.

Stability

Data are presented of three production scale batches tested under real time and accelerated conditions. Stability parameters are identical to the release specifications with exception of the determination of some impurities. Residual solvent, heavy metals and pesticides residues and aflatoxins were not tested because there are not generated during storage.
All specifications were met at all time points. The marker content remained stable and no changes were observed in the phytochemical fingerprint profile. The results support the proposed shelf life of 24 months and no special storage precautions are required.

II.2.3 FINISHED PRODUCT

Description and Composition of the herbal medicinal product
Diao Xin Xue Kang capsules contain 100 mg of a dried water extract (DER: 50-66.7:1) of the dried rhizomes of *Dioscorea nipponica* Makino. Besides the herbal preparation, the capsules also contain maize starch as filler. The capsules shells consist of hypromellose and titanium dioxide.

Manufacturing process
Diao Xin Xue Kang capsules are manufactured by Chengdu Diao Pharmaceutical Group Co., Chengdu, Sichuan, People's Republic of China. The manufacturer was inspected by the Dutch Inspectorate (IGZ) in November 2009, and in June 2012. IGZ confirmed that the production complies with (EU)GMP standards. The manufacturing process and in- process controls have been described adequately. A flow diagram summarizing the manufacturing process and in-process controls has been provided. In-process controls are appropriate considering the nature of the product and the method of manufacture.
Process validation performed with three production scale batches shows batch to batch consistency for TLC fingerprint, loss on drying, disintegration time, uniformity of mass and marker content.

Batch release of the finished medicinal product for the European Union is performed by Tjoapack B.V. (Emmen, Nederland). Tjoapack B.V. (Emmen, Nederland) is GMP-certified by the Dutch Inspectorate for batch releases in the EU. The company assured that all batches will be tested in accordance with established specifications.

Control of Excipients
Maize starch complies with its European Pharmacopoeia monograph. Satisfactory specifications were submitted for the capsule shell. The shells contain hypromellose and titanium dioxide. Both excipients comply with their respective Pharmacopoeial monographs. The capsule shells are produced in France.

Control of the finished product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, uniformity of mass, loss on drying, disintegration time, identification (chemical test and TLC), marker content and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided.

Analytical data of three production scale batches have been provided, demonstrating compliance with the specification.

Container closure system
The finished product is packed in PVC-aluminium blisters placed in a carton box. Specifications and certificates are provided from the manufacturers for all components. Submitted data are in compliance with the guideline on plastic immediate packaging materials. It is confirmed that all plastic materials comply with relevant EU legislation.

Reference Standards or Materials
Satisfactory characterization of the primary and working reference standards have been provided.

Stability
Overall - Studied parameters in the different stability studies were described sufficiently. Limit values are identical to these of the release specifications (except the tolerance interval for the marker which was 95 – 105% related to $t_{0,}$ which is acceptable). Analytical procedures are identical to those used for the testing of release specifications.
Real time and accelerated studies - Stability of the finished product was investigated with production batches at real time (three batches) and accelerated conditions (4 batches). The studies were performed in accordance with the relevant ICH guidelines. The results support the proposed shelf life of 24 months below 25 °C.

Conclusion
There are no objections for granting Diao Xin Xue Kang capsules a registration from a quality point of view.

II.3 SAFETY & SAFE USE

II.3.1 Non-clinical safety data

According to Article 16c (1)d of Directive 2001/83 safety should be justified by “a bibliographic review of safety data together with an expert report”.

In the course of the procedure, two expert reports written by nonclinical experts have been submitted to substantiate the safety of Diao Xin Xue Kang capsules. The expert reports included an overview of available safety data from literature, and information from the two main databases for Chinese scientific journals: VIP and China National Knowledge Infrastructure. All studies were conducted and published before Good Laboratory Practises was a regulatory requirement. On the basis of experimental details provided it was not possible to ascertain if the data assessed in the review would comply with today’s regulatory safety testing requirements with regards to design, conduct and analysis. However, preclinical data submitted did not indicate safety concerns. Because the longstanding use of the product is satisfactorily demonstrated, the lack of a complete standard pre-clinical safety package is considered acceptable and in compliance with the Guideline on non-clinical documentation for herbal medicinal products in applications for marketing authorization (bibliographical and mixed applications) and in applications for simplified registration (EMEA/HMPC/32116/05).
In view of the absence of adequate data from genotoxicity testing, the applicant has provided assurance that results of a genotoxicity test conducted in accordance existing EU guidelines will be provided before the renewal of the registration.

Interactions
Available scientific data does not indicate that extracts of *Dioscorea nipponica* have an effect on drug metabolizing enzymes. Nevertheless as a precautionary measure concomitant intake with other medicinal products is not recommended.

Pharmacokinetic studies:
Pharmacokinetic studies are not required according to the legislation for traditional herbal medicinal products.

Conclusion
From a pre-clinical viewpoint there are no objections for granting Diao Xin Xue Kang capsules a registration as a traditional herbal medicinal product. However, the registration holder is committed to submit results of a genotoxicity test conducted in accordance existing EU guidelines before the renewal of the registration.

II.3.2 Clinical Safety data

Data submitted consisted of reported adverse drug reactions within the Chinese pharmacovigilance. monitoring system, an overview of adverse events reported in clinical trials in humans performed in China and case reports. The MAH has provided an overview of side effects observed in 241 clinical studies performed in China which included more than 16000 patients. Adverse reactions were observed in 358 patients (2.2%). They included headache and dizziness, facial flushing, dry mouth, upper gastrointestinal discomfort (diarrhoea and constipation) and pruritus. No serious adverse reactions were reported.

The clinical data provided can only be considered as supportive because the studies were not incompliance with the existing EU guidelines. Moreover, as the studies were performed in China it is not clear to what extent the data can be extrapolated to the European population.
However the applicant has satisfactory demonstrated that extracts of *Discorea nipponica* have long history of safe use in China and in Russia (see below). Available clinical data supports the safety of Diao Xin Xue Kang capsules.
Furthermore, the MAH has provided assurance that after registration the safety of the product will be monitored with a Pharmacovigilance system. Results of safety monitoring will be submitted via Periodic Safety Update Reports.

Background of Safety Assessment:

An application for registration as traditional herbal medicinal product must be accompanied by, among others, a bibliographic review of safety data together with an expert report. Where required by the competent authority upon additional request further data necessary for assessing the safety of the herbal medicinal product should be added. Non-clinical tests are considered unnecessary, where the herbal medicinal product on the basis of the information on its traditional use proves not to be harmful in specified conditions of use. Additional data on the traditional use of the herbal medicinal product, e.g. marketing experience in another Member State shall be taken into account, because even a long tradition does not exclude the possibility that there may rise concerns with regard to the product's safety. Therefore, competent authorities are entitled to ask for all other data necessary to assess the safety.

II.4 JUSTIFICATION OF TRADITIONAL USE

According to Directive 2001/83 EC Art 16 (4)c traditional use shall be justified by bibliographical or expert evidence showing that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Community.

II.4.1 Evidence of Traditional Use

Extracts of the roots of *Dioscorea nipponica* Makino have a long history of medicinal use in China. The herb was first recorded in 1959 and in 1977 a monograph of *Dioscorea nipponica* Makino was included in the official Chinese Pharmacopoeia. Diao Xin Xue Kang capsules are marketed in China since 1970. During the past 30 years more than 100 million of patients have used the product. A product containing an extract *of Dioscorea nipponica* is on the Russian market since 1975. For the justification of traditional use in the European Union reference is made to European herbal handbooks, sales figures and documented use in France, Belgium, the Netherlands and the UK. The data supplied by the MAH adequately demonstrate the medicinal use of *Dioscorea nipponica* Makino root extracts for 30 years, of which 15 years in the European Community.

II.4.2.Proposed indication

The following indication has been accepted:

”Traditioneel kruidengeneesmiddel toegepast ter verlichting van hoofdpijn en bij spierpijn en spierkrampen in nek, rug en benen. De toepassing is uitsluitend gebaseerd op traditioneel gebruik en niet op klinisch bewijs.” (Traditional medicinal product for the relief of headache and muscular pains and muscle cramps in the neck, back and legs. This use is based on traditional use only and not on demonstrated clinical efficacy)

Efficacy

No clinical efficacy data are required for registration of Traditional Herbal Medicinal Products.
The indication is based on the use described in handbooks on Traditional Chinese Medicines and in European herbal handbooks.
Pharmacological data support the indication. Saponins, main constituents of Diao Xin Xue capsules, were found to induce smooth muscle relaxation in several animal models.

Conclusion

The data supplied by the MAH substantiates 30 years of medicinal use of *Dioscorea nipponica* Makino aqueous extract, including at least 15 years in the European Community and support the traditional use indication.

Background of Assessment on the basis of long-standing use and experience:

The long tradition of the herbal medicinal product makes it possible to reduce the need for clinical trials, in so far as the pharmacological effects or efficacy of the herbal medicinal product are plausible on the basis of long- standing use and experience.
Bibliographic or expert evidence is required to the effect that the herbal medicinal product, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of application, including at least 15 years within the European Union. Furthermore, the pharmaceutical effects or efficacy are plausible on the basis of long-standing use and experience.

In cases of doubt and at the request of the Member State where the application has been submitted, the Herbal Medicinal Products Committee shall draw up an opinion on the adequacy of the evidence of the long-standing use of the herbal medicinal product.

III OVERALL CONCLUSION AND RISK ASSESSMENT

This is an application for registration as a Traditional Herbal Medicinal Product, under article 16a of Directive 2001/83/EC.

The application of Diao Xin Xue Kang capsules was discussed in 5 Board meetings. In the first discussion which was in September 2, 2010, it was concluded that a full assessment of the pre-clinical safety data could not performed because the complete study reports of the available repeated dose toxicity, genotoxicity and reproduction toxicity studies were not be provided. Additional safety data provided by the MAH were discussed in the Board meeting of December 23, 2010. The MEB, decided that the pre-clinical safety data were insufficient because genotoxicity tests did not comply with existing guidelines. Furthermore, it was concluded that the submitted farmacovigilance data did not prove that the use of Diao Xin Xue Kang is safe due to strong limitations of the provided data.
New data provided be MAH were discussed in the Board meeting of September 1, 2011. It was concluded that the submitted clinical safety data were insufficient, because extrapolation of the data provided, concerning the use in patients and the safety as acquired in China, to the European population was inadequate. The MAH was asked to substantiate the extrapolation of safety data obtained in the Chinese population to the Western population and to provide more information on the extent of use (number of packages sold) in Europe.
The response of the MAH was discussed in the Board meeting of November 24, 2011 but no final conclusion was drawn. Discussion continued in the meeting of January 26, 2012. In this meeting, the MEB decided that, on the basis of the data submitted, a registration can be granted if the safety of the product is monitored with a Pharmacovigilance system and results of a genotoxicity test conducted in accordance existing EU guidelines are submitted before the renewal of the registration.

Quality
The quality data submitted with this application are satisfactory

Safety
A satisfactory review of the available safety data has been provided. The presented data indicate no safety concerns. Assurance was provided that additional results of genotoxity testing will be provided before renewal of the registration. Based on the documented used for a period exceeding 30 years this is considered acceptable.

Efficacy
No clinical efficacy data are required for registration of Traditional Herbal Medicinal Products. Clinical efficacy has not been assessed for this indication and a regular Benefit-Risk balance has not been established.

Traditional use
The MAH has provided a bibliographic review demonstrating that *Dioscorea japonica* aqueous extracts have been in medicinal use for 30 years, including 15 years in the European Community.

Classification
The herbal medicinal product is classified as a non prescription product and for UAD (Uitsluitend Apotheek en Drogist), which means that sale is restricted to only pharmacies or drugstores.

SPC, PIL and labelling
The SPC, PIL's and labelling are satisfactory.

Marketing authorisation
The MEB, on the basis of the data submitted, considered that Diao Xin Xue Kang, capsules for oral use demonstrated adequate evidence of traditional use, quality and safety, and therefore can be registered. Diao Xin Xue Kang, capsules for oral use has been registered in the Netherlands with the following indication: "*Traditioneel kruidengeneesmiddel toegepast ter verlichting van hoofdpijn en bij spierpijn en spierkrampen in nek, rug en benen. De toepassing is uitsluitend gebaseerd op traditioneel gebruik en niet op klinisch bewijs".*
The date for the first renewal will be: 15 March 2017

List of abbreviations

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
GMP	Good manufacturing practice: part of a quality system covering the manufacture and testing of active pharmaceutical- ingredients and -products.
MAH	Marketing Authorisation Holder
Ph. Eur.	European Pharmacopoeia
TLC	Thin Layer Chromatography

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	RVG	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached