Public Assessment Report

Kaloba druppels, drops for oral use
Dr. Willmar Schwabe GmbH, Germany

RVG 34174

NL-PAR
TRADITIONAL HERBAL MEDICINAL PRODUCT

Route of administration:	oral
Prescription status:	non-prescription, algemene verkoop
Therapeutic indication:	Traditioneel kruidengeneesmiddel bij verkoudheid. De toepassing is uitsluitend gebaseerd op langdurige gebruikservaring.
Date of authorisation in NL:	11 June 2007
Application type/legal basis:	Directive 2001/83 article 16a

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I LAY SUMMARY

The Medicines Evaluation Board (MEB) has granted Dr. Willmar Schwabe from Germany a marketing autorisation for Kaloba druppels, drops for oral use as a Traditional Herbal Medicinal Product (Registration number: RVG 34174). This product is available without prescription as general sales (Algemene Verkoop).

The active ingredient of Kaloba is obtained from *Pelargonium sidoides* roots. It is used as "*Traditioneel kruidengeneesmiddel bij verkoudheid. De toepassing is uitsluitend gebaseerd op langdurige gebruikservaring"* Traditional herbal medicinal product for common cold, based on traditional use only.

This registration is based exclusively upon the longstanding use of *Pelargonium sidoides* root as a traditional herbal medicinal product. For a Traditional Herbal Registration there is no requirement to assess clinical trials that scientifically prove that the product works.

The requirements in the three most important areas of assessment (traditional use, quality and safety) are fulfilled 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 CBG-MEB granted a registration as traditional herbal medicinal product for Kaloba from Dr. Willmar Schwabe, Germany. This product is classified as AV (Algemene Verkoop), which means that sale is not restricted to only pharmacies or chemist's.

This product consists of a solution of a liquid ethanolic extract of the root of *Pelargonium sidoides.* This product is indicated "*Traditioneel kruidengeneesmiddel bij verkoudheid. De toepassing is uitsluitend gebaseerd op langdurige gebruikservaring"* Traditional herbal medicinal product for common cold, based on traditional use only.

The data supplied by the MAH substantiates 30 years of medicinal use of *Pelargonium sidoides*, including at least 15 years in the European Community. A satisfactory review of the available safety data on *Pelargonium sidoides* has also been provided, together with an Expert Safety Report supporting the proposed product.

At the time of assessment and registration a Community Herbal Monograph of Pelargonium sidoides was not yet established.

At the time of assessment there were no preparations of *Pelargonium sidoides* registered on the Dutch market. Within the EEA the same product is authorised in Germany under the name Umckaloabo®.

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 Herbal Monograph or 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:	*Pelargonium sidoides* DC
Family:	Geraniaceae
Parts of plant used:	Roots (dried)
Origin:	South Africa

Manufacture

The plant is grown in the wild or cultivated in South Africa. The roots are washed, cut and dried. Production of the herbal substance is adequately documented.

Control of herbal substance

The crude plant material complies with the requirements of an in-house monograph which includes specifications for identity (macroscopic and microscopic description, TLC test), purity (foreign matter, ash, loss on drying, heavy metals, residual pesticide levels, aflatoxins levels and microbiological purity) and content (total phenols). Specifications are in accordance with Ph. Eur. requirements where appropriate or otherwise justified.

Analytical testing meets the requirements of the Ph. Eur. where appropriate or has been otherwise justified and validated.

Reference Standards or Materials

Satisfactory Certificates of Analysis for the primary reference standards have been provided.

Stability

The MAH has made a commitment that the herbal substance is tested directly before further processing, so therefore no stability data are required.

II.2.2 HERBAL PREPARATION

General information

Herbal preparation:	Pelargonium sidoides dry root extract
Scientific name of the plant:	*Pelargonium sidoides DC*.
Parts of the plant used:	root
Extraction solvent:	ethanol 11% (m/m)
Drug Extract Ratio (DER):	1: 8-10

Manufacture

The herbal preparation is produced under GMP (Good Manufacturing Practice) conditions. A detailed description of the manufacturing process (extraction, drying, milling and homogenisation), including batch size, manufacturing formula, process conditions, in process controls and flow diagram, has been provided and is satisfactory.

The in-process controls and specifications are sufficiently detailed, and justified.

Control of the herbal preparation

The specifications for the herbal preparation have been laid down in an in-house monograph. Release specifications for the extract comprise appearance, TLC fingerprint, relative density, microbial purity, dry residue, contents of total phenol and ethanol. Specifications are in accordance with Ph. Eur. requirements where appropriate or otherwise justified.

Analytical testing meets the requirements of the Ph. Eur. where appropriate or has been otherwise justified and validated.

Certificates of analysis of three production-scale batches of extract were presented. All data comply with the established specifications.

Reference Standards or Materials
Satisfactory Certificates of Analysis for the primary reference standards have been provided.

Container closure system
The suitability of the container closure system was sufficiently demonstrated.

Stability
Three production-scale batches were tested during three months at real time-, intermediate- and accelerated conditions. Specifications tested are identical to the release specifications, with a tolerance interval for the content values of 95 – 105% related to t_0. Stability was demonstrated for at least one month at long term- and at least one week at intermediate and accelerated conditions. This is considered to be acceptable since the active substance is stored for 3 days (weekend) at most before further processing.

II.2.3 FINISHED PRODUCT

Description and Composition herbal medicinal product
The product is an oral liquid preparation with an alcoholic aqueous extract from the roots of *Pelargonium sidoides* as pharmaceutically active component, which is contained in the finished product at a ratio of 80%. Glycerol 85% is used as a solvent/preservative. In addition to its function as extraction solvent, the ethanol contained in the extract acts as a preservative in combination with glycerol. The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs.

Manufacturing process
A flow diagram of the production process was included in the dossier. The manufacturing process and in-process controls have been adequately described.
In-process controls are appropriate considering the nature of the product and the method of manufacture.

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, identity (TLC; HPLC – glycerol and ethanol), purity (relative density, microbial quality, pH value, dose and uniformity of dose) and contents of active substance/ total phenols, glycerol and ethanol. 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.
Batch analytical data 3 batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Container closure system
The container consists of a brown screw-top glass bottle with a white drop dispenser and white screw cap. The brown glass bottle Type III meets the requirements of Ph. Eur. 3.2.1. "*Glass containers for pharmaceutical use*". Fill sizes are 20, 50 ml and 100 ml.
From the (technical) data submitted it can be concluded that the used plastic materials meet the requirements of the relevant Ph. Eur. monographs on materials for pharmaceutical use and the applied colouring agents are allowed in contact with foodstuffs.

Reference Standards or Materials
Satisfactory Certificates of Analysis for the primary 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 90 – 105% related to t_0 which is acceptable. Analytical procedures are identical to these used for the testing of release specifications.

Real time, intermediate and accelerated studies - Stability of the finished product was investigated on each of the package sizes at real time, intermediate and accelerated conditions. The studies were performed in accordance with the relevant ICH guidelines. Based on the results available so far a shelf-life of 2 years was granted, with the storage condition "*Do not store above 30ºC*".

In-use stability - Stability after opening was investigated on two batches each, of both the smallest and the largest pack sizes. The studies were performed according to the relevant ICH guidelines, except that the test was not performed with batches that were at the end of their shelf-life. On the basis of the submitted results an in-use stability of 3 months was accepted for packages of 20 and 50 ml and 6 months for packages of 100 ml. The MAH has committed to submit in-use stability data for an additional batch tested towards the end of its shelf-life as soon as available.

Photostability - The photostability of the finished product was investigated in accordance with the "*Note for Guidance on the Photostability Testing of New Active Substances and Medicinal Products*". The finished product was demonstrated to be photostable with respect to all of the relevant specifications.

Conservation effectiveness - Testing for adequate conservation was performed on two samples from two different production-scale batches (after shelf-lives of 36 and 24 months, respectively) in accordance with Ph. Eur. 5.1.3 "*Efficacy of antimicrobial preservation*". In this way the efficacy of the preservation has been demonstrated.

TSE statement

A transmission of TSE (bovine spongiform encephalitis) can be excluded as glycerol 85% is exclusively of vegetal or mineral-synthetic origin (written confirmation by the manufacturer has been submitted).

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”.

A bibliographic review of non-clinical data (both published and unpublished), including toxicological information, is presented. Also an expert report written by a non-clinical expert has been submitted.

Toxicity studies:
The submitted scientific references on single-dose and repeated dose toxicity show that the extract of *Pelargonium sidoides* is very well tolerated in animal studies in doses comparable to the adviced daily dose for humans and beyond that.
Extensive marketing experience with the corresponding product Umckaloabo® did not reveal any genotoxic and carcinogenic potential. The lack of carcinogenicity studies has been justified sufficiently.
Study results indicated that the *Pelargonium sidoides* extract has no effect on fertility and embryo-foetal development. However, as no specific reproduction studies are available in humans, a statement has been included in SPC and package leaflet that *Pelargonium sidoides* extract should not be taken during pregnancy and lactation.
For local tolerance and immunotoxicity no data have been found in scientific literature. However, longterm experience with the product demonstrates no safety concerns.
Hepatotoxicity could not be traced in scientific literature and neither was it detected in a hepatotoxicity study conducted by the MAH, in doses comparable to the adviced daily dose for humans and beyond that.

Interactions
In the only published interaction study that was found, no influence on warfarin pharmacokinetics was detected. There are no further indications of any interaction with other medicines.

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

Conclusion
From the presented non-clinical data it is concluded that Kaloba® can be safely used.

II.3.2 Clinical Safety data

Whereas clinical data are not obligatory for demonstration of efficacy, they are of use to justify the safety of the product, because side-effects might be reported. A total of 5 clinical studies derived from a literature search in PUBMED and MEDLINE databases were provided by the MAH and have been evaluated for safety aspects. All these studies concern the corresponding product. Furthermore the extensive unpublished pharmacovigilance database of the corresponding product, that is available to the MAH, together with safety data from so far unpublished clinical studies which are included in this database, have been evaluated.

No side effects could be related to the use of *Pelargonium sidoides* extract. As a precaution a contraindication has been taken up for hypersensitivity. Due to the lack of experience *Pelargonium sidoides* should not be used during pregnancy and lactation. For children from 1 year and up sufficient safety data have been presented.
Pelargonium sidoides has no or negligible influence on the ability to drive and use machines.

Long-term experience:
Long-term experience with the corresponding product did not give reason for any safety concerns. In the period 1994-2005 240 million defined daily doses were marketed in Germany.

Conclusion

The presented data, together with the extensive marketing experience of the corresponding *Pelargonium sidoides* DC preparation demonstrate that Kaloba® can be safely used.

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.

At the time of assessment and registration a Community Herbal Monograph on *Pelargonium sidoides* was not yet established.

Evidence of Traditional Use
For the justification of traditional use reference is made to a pharmacopoeia, scientific literature, herbal Materia Medica's, a draft WHO monograph and an expert statement on the extent of use.

The data supplied by the MAH demonstrate clearly 30 years of medicinal use of Pelargonium sidoides root. Reference has been made to the corresponding product Umckaloabo® which contains an extract of *Pelargonium sidoides* DC and has been listed on the German "Rote Liste" (an annual list of medicines available in Germany) from 1975 until 2005. In this way also the medicinal use of 15 years in the European Community has been satisfactory proven.

Proposed indication
The following indication has been accepted:

"*Traditioneel kruidengeneesmiddel bij verkoudheid. De toepassing is uitsluitend gebaseerd op langdurige gebruikservaring*".

Efficacy
No clinical efficacy data are required for registration of Traditional Herbal Medicinal Products.

Conclusion
The data supplied by the MAH substantiates 30 years of medicinal use of *Pelargonium sidoides DC* root, including at least 15 years in the European Community and support the traditional 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.
Bibiographic 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.

Quality
Kaloba® druppels, drops for oral use have a proven chemical-pharmaceutical quality.

Safety
A satisfactory review of the available safety data has been provided. The presented data demonstrate that Kaloba® can be safely used.

Efficacy
No clinical efficacy data are required for registration of Traditional Herbal Medicinal Products.

Traditional use
The MAH provided a bibliographic review with adequate evidence that the extract of *Pelargonium sidoides* DC root has 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 AV (Algemene Verkoop, general sale), which means that sale is not restricted to only pharmacies or drugstores. This was based on the fact that the use of the product does not imply any risk, there has been a broad experience in use, the indication is suitable for general sale and the period of use is limited.

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

Marketing autorisation
The MEB, on the basis of the data submitted, considered that Kaloba® druppels, drops for oral use demonstrated adequate evidence of traditional use, quality and safety, and therefore granted a marketing authorisation. Kaloba druppels, drops for oral use has been registered in the Netherlands on 11 June 2007 with the following indication: "*Traditioneel kruidengeneesmiddel bij verkoudheid. De toepassing is uitsluitend gebaseerd op langdurige gebruikservaring*".

The date for the first renewal will be: 11 June 2012.

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
HPLC	High Pressure Liquid 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
Change of address of the marketing authorisation holder.	34174	IA	3-6-2009	6-7-2009	Approval	N
Change to batch release arrangements and quality control testing of the finished product.	34174	IA	3-6-2009	28-7-2009	Approval	N