LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Flexagil, cream

(*Symphytum officinale* L., [comfrey] root, liquid extract)

SE/H/787/01//DC

This module reflects the scientific discussion for the approval of Flexagil, cream. The procedure was finalised at 2008-11-17. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

CCS, Clean Chemical Sweden AB, has been granted a marketing authorisation for Flexagil, cream, 35 %. The active substance is a pyrrolizidine alkaloid-free ethanol-water extract of fresh comfrey (*Symphytum officinale* L.) root. The active substance in Flexagil has a well-established medicinal use with a recognised efficacy and an acceptable level of safety according to article 10a of Directive 2001/83/EC. The non-clinical and clinical parts of the submitted documentation are bibliographical. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Flexagil is presented in the form of a cream containing 35 g of pyrrolizidine alkaloid (PA)-reduced liquid extract of comfrey root per 100 g cream. The excipients are: purified water, arachis oil (peanut oil), cetostearyl alcohol, glycerol monostearate (E471), sodium dodecyl sulphate, perfume oil Spezial PH 032791 (including bergamot oil and benzyl benzoate), spruce needle oil, lavender oil, Emulgin L, sodium hydroxide and Phenonip (phenoxyethanol, methyl parahydroxybenzoate (E218), butyl parahydroxybenzoate, ethyl parahydroxybenzoate (E214), propyl parahydroxybenzoate (E216))
The cream is filled in aluminium tubes (50 and 100 g) with a plastic screw cap.

II.2 Drug Substance

The herbal substance is *Symphytum officinale* L. (comfrey) root; fresh roots are used to prepare the extract. The origin of the *Symphytum* plants used for extraction is either biologically cultivated from Germany or collected from the wild in the Balkans.
The herbal preparation is the pyrrolizidine alkaloid (PA)-reduced liquid extract of comfrey root (1:2) (extraction solvent: ethanol 60% v/v).

Comfrey root does not have a monograph in the Ph Eur, the in-house monograph refers to the monograph *Comfrey root* in DAC (*Deutscher Arzneimittel Codex*, 1979).

Relevant information on tests on macroscopic and microscopic identification of the roots and the exclusion of other species of comfrey that have similar morphologic features is presented. The route of extraction has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the acceptance limits have been justified. As it is a PA-reduced extract, the specification also contains a specified limit of pyrrolizidine alkaloids. The analytical methods applied are suitably described and validated and the description of the manufacturing process and process controls of the extract is sufficient.

Stability studies under ICH conditions have been conducted with the herbal substance and the herbal preparation and the data provided are sufficient to confirm a shelf-life of 24 months at a storage temperature below 30ºC.

II.3 Medicinal Product

Flexagil, cream, 35 % is formulated using excipients described in the current Ph Eur, except for Phenonip and Perfume oil spezial PH 032791 which are controlled according to acceptable in house specifications, glycerol monostearate which is controlled according to DAC (*Deutscher Arzneimittel Codex*) and spruce needle oil which is controlled according to DAB (*Deutsches Arzneimittel Buch*). All raw materials used in the product are of vegetable origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with special storage precautions not to be stored above 30ºC.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Anti-inflammatory activity following oral or parenteral administration of extracts of ethanolic and aqueous extracts of the root of *Symphytum officinale* L. have been demonstrated in different *in vitro* and animal model studies. Anti-inflammatory activity has also been reported for certain ingredients such as rosmarinic acid and a glycopeptide. No reports on anti-inflammatory activity on topical application have been submitted.

III.2 Pharmacokinetics

Very little information on the actual extract is available.

Symphytum officinale L. root contains small amounts, 0.3-0.4 %, of pyrrolizidine alkaloids and their N-oxides. Pyrrolizidine alkaloids can be divided into two groups based on their structure; unsaturated pyrrolizidine alkaloids (toxic after metabolisation) and saturated pyrrolizidine alkaloids (considered non-toxic). The pyrrolizidine alkaloids in *Symphytum officinale* L. occur mostly as N-oxides (non-toxic or low toxicity).

The percutaneous absorptions of pyrrolizidine alkaloids were investigated in rats by Brauchli et al. 1982. The excretion of pyrrolizidine alkaloids in the urine during 2 days was in the range of 0.1-0.4 % of the dose. It was concluded that the dermally absorbed N-oxides were not or only to a small extent converted to the free alkaloids in the organism. The oral application led to a 20-50 times higher excretion of N-oxides and free alkaloids in the urine.

Results from an *in vitro* study on human skin, indicated that the absorption of pyrrolizidine alkaloids (monocrotaline) is low.

III.3 Toxicology

In the original application no toxicological studies had been performed on Flexagil cream or the extract contained in it. Since no genotoxic data of the actual substance/herbal preparation had been submitted the applicant was asked to submit such data. The applicant has provided results from an Ames test (Reverse Mutation assay using *Salmonella typhimurium* strains). The highest dose level used (5µL/plate) was the maximum required by the OECD guidelines. The results obtained in the study showed that the product specific extract is not mutagenic in Ames test.

Symphytum officinale L., as some other plants, contains pyrrolizidine alkaloids. The toxicity (e.g. hepatotoxicity) of pyrrolizidine alkaloids with a 1,2-unsaturated necine structure is well recognised. The extract of the root of *Symphytum officinale* L. contained in Flexagil cream has been treated to remove pyrrolizidine alkaloids. The content of pyrrolizidine alkaloids in the extract (herbal substance) contained in Flexagil cream is low, ≤1 ppm (specification). The finished product, Flexagil cream, contains at maximum 0.35 ppm pyrrolizidine alkaloids, which is not considered to pose a safety concern at recommended dosage.

III.4 Ecotoxicity/environmental risk assessment

No information is given. Generally, herbal medicinal products are unlikely to result in any significant risk to the environment due to the nature of their constituents (CHMP guideline on environmental risk assessment, 2006).

III.5 Discussion on the non-clinical aspects

It is known that the herb *Symphytum officinale* contains toxic and carcinogenic pyrrolizidine alkaloids. However, during the preparation of the product specific extract these alkaloids are removed. The amount of the pyrrolizidine alkaloids in the finished product Flexagil is less than 0.35 ppm, which is not considered to pose a safety concern at recommended dosage.

The product specific extract was non-mutagenic in the Ames test.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

No data available.

IV.2 Pharmacodynamics

The mechanism of action is not known.

In the pharmacodynamics section in the SPC, the following information has been included: “In limited clinical trials, the active substance in Flexagil, cream has been found to reduce pain due to joint injuries.”

IV.3 Clinical efficacy

Three main studies (Graubaum 2006; Predel 2005; Koll 2000), in which Flexagil has been tested against placebo or diclofenac, have been submitted.

In the study by Graubaum (110 patients Flexagil, 110 patients placebo), Flexagil had a significantly better effect than placebo on the primary efficacy parameter (sum of pain at rest and on movement) i.e. 55% versus 11% pain reduction, in patients with knee osteoarthritis. Similar effects were seen on all secondary parameters (VAS-pain, WOMAC, severity, CGI, efficacy index).

In Predel (2005), Flexagil was tested against topical diclofenac in 82 + 82 patients with sprained ankle. Primary efficacy variable was the AUC of the pain reaction to pressure. Secondary parameters included circumference of joint, pain sensation at rest and at movement (VAS), movement impairment, consumption of rescue medication, CGI. The 95% confidence interval for the primary efficacy parameter of Flexagil was completely above the margin of non-inferiority for diclofenac. All secondary efficacy parameters confirmed that Flexagil was not inferior to diclofenac.

Koll et al. (2000) tested the efficacy of Flexagil versus placebo in 80 + 60 patients with ankle sprains. Primary efficacy endpoint was tenderness in the ankle joint measured by tonometry and quantified as the AUC of the time/pressure curve. The secondary endpoints included reduction of ankle circumference and global assessment of efficacy by investigator and patients. Compared to placebo (AUC = 6.7), Flexagil (AUC = 5.0) was superior regarding reduction of pain ($p<0.0001$). Concerning reduction of ankle circumference, Flexagil (-6.4cm) was superior to placebo (-3.8cm) ($p = 0.0012$). The global efficacy assessment by both investigator and patient favoured Flexagil over placebo.

IV.4 Clinical safety

The number of adverse events in clinical trials is low and they have all been classified as non-serious. In the PSUR for a corresponding product for the years 2001-2006 it has been estimated that the product has been used by approximately 8 million patients during these 6 years. 19 spontaneous adverse reaction reports were filed during the period (mainly allergic skin reactions). There are no signals of clinical safety concerns in spite of an extensive clinical use of the active ingredient since the authorisation in 1966 in Germany.

IV.5 Discussion on the clinical aspects

In summary, the submitted studies all indicate clinical efficacy of Flexagil in reducing painful conditions of joints. The studies appear reasonably well performed, albeit not very large and only Koll (2000) according to GCP. Extensive clinical use of the active ingredient has been documented. No signals of clinical safety concern have been identified during this use or in the submitted clinical studies. The active ingredient is authorised in corresponding medicinal products in Germany (1966) and UK (2007).

The following therapeutic indication was accepted for Flexagil: “Herbal medicinal product for symptomatic relief of local pain conditions of mild to moderate intensity in connection with minor joint injuries of small and middle-size joints.”

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet could have been better designed, and the discussion of the results obtained in the test could have been more detailed, but the PL is considered acceptable.

The risk/benefit ratio is considered positive and Flexagil cream is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Flexagil, cream, 35 % was successfully finalised on 2008-11-17.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se