

European Practice: Experiences with a Risk-Benefit Analysis of HMPs for the Elaboration of ESCOP Monographs

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E/S/C/O/P

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H.**
beraten · analysieren · handeln

ESCOP

European Scientific Cooperative on Phytotherapy

- Founded in Cologne on 18 June 1989

Objectives

- Creation of harmonised criteria for efficacy and safety
- Preparation of scientific monographs
- Contribution to the acceptance of phytotherapy on a European level

ESCOP

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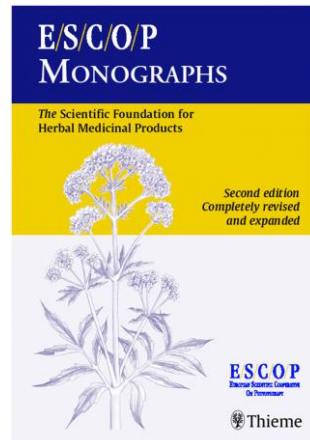
Monographs with the format of a Summary of Product Characteristics (SPC)

- Definition
- Constituents
- Clinical particulars
 - Therapeutic indication
 - Posology and method of administration
- Contra-indications
- Special warnings and special precautions for use
- Interaction with other medicaments and other forms of interaction
- Pregnancy and lactation

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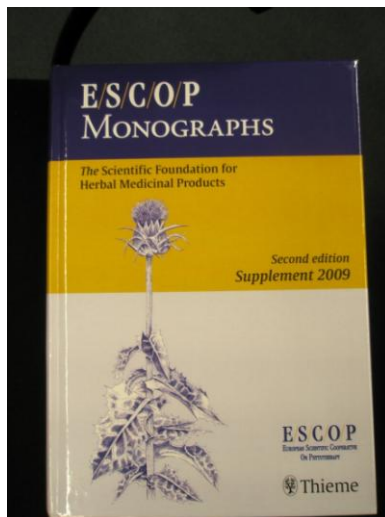
Monographs with the format of a Summary of Product Characteristics (SPC)

- Effects on ability to drive and use machines
- Undesirable effects
- Overdose
- Pharmacological properties
- Pharmacodynamic properties
 - in vitro experiments
 - in vivo experiments
 - pharmacol. studies in humans
 - clinical studies
- Pharmacokinetic properties
- Preclinical safety data
- References



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ESCOP Supplement 2009



to be ordered from:

www.escop.com

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ESCOP Supplement 2009

- AGRIMONIAE HERBA
- ALOE BARBADENSIS
- ANGELICAE RADIX
- BALLOTAE NIGRAE HERBA
- CAPSICI FRUCTUS
- CENTELLAE ASIATICAE HERBA
- CRATAEGI FRUCTUS
- CUCURBITAE SEMEN
- CURCUMAE XANTHORRHIZAE RHIZOMA
- CYNARAE FOLIUM
- ECHINACEAE ANGUSTIFOLIAE RADIX
- ECHINACEAE PALLIDAE RADIX
- ECHINACEAE PURPUREAE HERBA
- ECHINACEAE PURPUREAE RADIX
- ELEUTHEROCOCCI RADIX
- FUMARIAE HERBA
- GRAMINIS RHIZOMA
- GRINDELIAE HERBA
- HARPAGOPHYTI RADIX
- LAVANDULAE FLOS/AETHEROLEUM
- MALVAE FLOS
- MELALEUCAE AETHEROLEUM
- MILLEFOLII HERBA
- OLIBANUM INDICUM
- PAULLINIAE SEMEN
- PRUNI AFRICANAE CORTEX
- RATANHIAE RADIX
- ROSAE PSEUDO-FRUCTUS
- Silybi Mariani Fructus
- SYMPHYTI RADIX
- VACCINII MACROCARPI FRUCTUS
- VALERIANAE RADIX
- VIOLAE HERBA CUM FLORE
- VITIS VINIFERAE FOLIUM
- ZINGIBERIS RHIZOMA

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ESCOP Monographs

Importance of a Risk-Benefit Analysis

- Benefit and risk must be addressed adequately and included in the monograph (impact on patients' information)
- Risks >> benefit: no monograph
- Benefit must outweigh risk
- Better: benefit-risk-analysis

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ESCOP Monographs

Procedure of a Risk-Benefit Analysis during preparation of monographs

- Step 1 (Benefit): Available data from studies, bibliography, monographs, textbooks, expert reports, experience etc.
- Step 2 (Risk): Available data from studies, bibliography, monographs, textbooks, case reports etc.

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ESCOP Monographs

Evaluation of the Benefit

- Clinical data sufficient to justify a well-established medicinal use?
- If not, data on medicinal use and experience available?
- In the latter case: "soft" indications plus disclaimer: *"Efficacy in these indications is plausible on the basis of human experience and long-standing use."*

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"Well-established medicinal use"

Regulatory Requirements

- HMPC Guideline on the Assessment of Clinical Safety and Efficacy (adopted September 2006)
- "At least one controlled clinical study" (incl. e.g. post-marketing study) "of good quality"
- If clinical experience is well-documented and conclusive (human) pharmacological data available: case-by-case assessment

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ESCOP Monographs

Examples well-established medicinal use

- *Harpagophyti radix*: "Symptomatic treatment of painful osteoarthritis [14-27]; relief of low back pain [25-35]. - On the basis of its bitter tonic properties, devil's claw root is also widely documented as a remedy for loss of appetite and dyspepsia [36-43]."
- *Silybi marianae fructus*: "Toxic liver damage; supportive treatment in patients with chronic inflammatory liver conditions and hepatic cirrhosis [18-28]."

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ESCOP Monographs

Examples traditional use

- Grindeliae herba: "*Productive cough; catarrhs of the upper respiratory tract [...]*" plus disclaimer
- Agrimoniae herba: "*Locally as a gargle for inflammation of the oral and pharyngeal mucosa and as a compress or rinse to support the healing of wounds [...]*" plus disclaimer
- Tormentillae rhizoma: "*Unspecific acute diarrhoea. Adjuvant treatment of acute and subacute enteritis and colitis. Slight irritations of the mucosa of mouth and throat [...]*" plus disclaimer

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ESCOP Monographs

Evaluation of the Risk

- Collection and assessment of data from studies, bibliography, monographs, textbooks, case reports etc. if relevant for the use
- Presentation of data under:
 - ✓ Preclinical safety data and/or
 - ✓ Clinical safety data

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ESCOP Monographs

Evaluation of the Risk

- Appropriate information in the monograph e.g.
 - ✓ Contra-indications
 - ✓ Special warnings and special precautions for use
 - ✓ Interaction with other medicaments and other forms of interaction
 - ✓ Pregnancy and lactation
 - ✓ Effects on ability to drive and use machines
 - ✓ Undesirable effects
 - ✓ Overdose

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Examples for Risk Information

Echinaceae purpureae herba: "Hypersensitivity to plants of the Compositae. As with all immunostimulants, not recommended in cases of progressive systemic disorders and autoimmune diseases such as tuberculosis, leucoses, collagenoses, multiple sclerosis, AIDS or HIV infections [...]."

Melaleucaea aetheroleum: "In a few individuals, cases of allergic contact dermatitis after external application have been reported in the literature [...]. This is presumed due to degradation products formed on ageing of preparations [...]."

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Examples for Postulated Risks not included (I)

- Lini semen: *"In spite of its content of cyanogenic glycosides, single doses up to 150 - 300 g of powdered linseed are not toxic. Health risks are not to be expected [...]"*
- Allii sativi bulbus: *"In 10 healthy volunteers the use of garlic caplets taken 2 times daily (acc. to the authors roughly equivalent to two 4-g cloves of garlic daily) reduced the mean saquinavir area under the curve (AUC) during the 8-h dosing interval by 51 %, the saquinavir trough levels 8 h after dosing by 49 % and the mean maximum concentrations (C_{max}) by 54 %. After a 10-day washout period, the AUC, trough, and C_{max} values returned to 60 % - 70 % of their values at baseline [Piscitelli et al. 2002]."*

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Examples for Postulated Risks not included (II)

- Symphyti radix: *The pyrrolizidine alkaloids (PAs) in comfrey root are considered to be toxic, especially after oral ingestion [6, 10, 44-60]. However, processes are available to remove over 99 % of PAs during the production of extracts from comfrey root, enabling preparations for topical application to contain less than 0.35 ppm of pyrrolizidine alkaloids [18]. The use of such preparations, as exemplified by the clinical studies summarized above, is considered to have an acceptable level of safety [61].*
- Orthosiphonis folium: *"One case of hepatitis after intake of a product containing powdered Green tea and Java tea was reported but a causal relationship between hepatitis and the intake of Java tea could not be established [Garcia-Moran 2004]."*

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ESCOP Monographs

Results of the Risk-Benefit Analysis

- Benefit >> Risk (positive)

Preparation of a monograph with relevant information for use in specified indications as well as appropriate risk information for the safe use

Balance of benefit and risk even more important in case of low density of efficacy/traditional use data (lower indications levels)

- Benefit << Risk (negative): no monograph

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Efficacy Assessment

Example ESCOP Monograph: Nettle Root

Definition

Nettle root consists of the whole, cut or powdered, dried roots and rhizomes of *Urtica dioica* L., *Urtica urens* L., their hybrids or mixtures of these.

The material complies with the Deutsches Arzneibuch [1].

Clinical particulars

Therapeutic indications

Symptomatic treatment of micturition disorders (dysuria, pollakisuria, nocturia, urine retention) in benign prostatic hyperplasia (BPH) [25-50] at stages I and II as defined by Alken [51] or stages II and III as defined by Vahlensieck [50].

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Nettle Root - *Urticae radix*

- HMPC Draft Public Statement (16 July 2009)
- No traditional use ("BPH is a disease which cannot be treated without medical control")
- No well-established medicinal use ("no such study of good quality can be found in the literature")
- Solution? Sufficient (human) pharmacological data? Traditional use after initial diagnosis?
- E.g., UK Saw Palmetto in BPH symptoms ("who have a confirmed diagnosis...")

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EU Commission 2010

"The HMPC welcomed the legal interpretation received from the European Commission concerning the provisions of Article 16a(1)(a) of Directive 2004/24/EC, regarding the possibility for the indications of traditional herbal medicinal products to refer to a prior medical diagnosis with a view to excluding serious conditions, thus ensuring that patients safely self-medicate. Such medical diagnosis can be remote in time from the decision to take a traditional herbal medicine. **Community herbal monographs with indications relating to traditional use may refer to a prior medical diagnosis intended to prevent treatment of more serious pathologies with traditional herbal medicinal products.** In any case, the traditional herbal medicinal product still needs to be intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment. The traditional herbal medicinal product has to be a non-prescription medicine."
(Report HMPC Meeting 14 – 15 July 2010)

Impact on group assessment of herbal drugs used in BPH?

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Current ESCOP Projects

Revision of existing monographs

Elaboration of monographs for less well-documented plants (lower indication level, low risk) e.g.

- Alchemillae herba
- Leonuri herba
- Marrubii herba
- Menyanthidis folium
- Tormentillae rhizoma

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Conclusion and Perspectives

- ESCOP monographs do include a well-substantiated **benefit-risk** analysis
- Relevant information for use (indications) and appropriate risk information for the safe use
- Balance of benefit and risk more important in case of low density of efficacy data (lower indications levels)
- Next steps for ESCOP: Online publication of monographs (Cimicifugae rhizoma as a pilot project)

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