



HERBAL MEDICINES

- 👉 Many herbal medicines have a long tradition of use in clinical practice
- 👉 Within the EU, herbal medicines must be approved prior to marketing to ensure that they are of acceptable safety and quality
- 👉 A national simplified “traditional-use registration” process for traditional herbal medicines has been introduced in EU member states
- 👉 More than 160 harmonised “community” herbal monographs that contain clinical, safety, dosage and interaction data, have also been developed and are publicly available

INTRODUCTION

Herbal medicines have been used for thousands of years and have increased in popularity over the years; recent studies have estimated usage of 30% and 12-14% of consumers in the UK and USA respectively.^{1,2} Although they are often regarded as being safe because they are “natural”, there have been several reported incidences of serious adverse reactions, resulting from use of certain herbal substances, including renal failure with *Aristolochia* species and hepatic failure with kava kava.^{3,4}

Many patients take herbal medicines, frequently without consulting their doctor or other healthcare professional.^{1,2} In addition, patients taking herbal medicines may also be taking conventional medicines, increasing the risk for herb-drug interactions (e.g. risk of bleeding with ginkgo and some anti-thrombotic agents; risk of transplant rejection with St John's Wort and some immunosuppressants).^{2,5,6}

Although many herbal medicines on the market may have a long tradition of use, not all have undergone the same standard testing required for the authorisation of conventional medicines and therefore would not be eligible for a full marketing authorisation.⁷ The European Herbal Directive 2004/24 facilitated the introduction of a simplified registration procedure (**traditional-use registration** (TUR)) for herbal medicines that fulfil certain criteria.⁷ Herbal medicines eligible for TUR do not have to meet the same requirements as the conventional marketing authorisation (licence) for other medicines.⁸ The Directive also introduced a **process of harmonisation of information for all herbal medicines** (by way of community monographs).^{7,9}

This bulletin provides information on these EU developments, including the TUR procedure for herbal medicines and the development and role of community herbal monographs.

TERMINOLOGY

Within the EU, a medicine (termed a **medicinal product**) is defined as “any substance or combination of substances presented as having properties for treating or preventing disease in human beings *or* any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis”.^{10,11} **This definition applies to all medicines, including those derived from chemical, biological and herbal sources.**

While many medicines in clinical practice have originated from a herbal source (e.g. opiates from the opium poppy and digoxin from foxglove), they are not considered to be herbal medicines because they have been extracted, isolated, purified and/or formulated in the same way as medicines derived from synthetic sources (e.g. paracetamol).^{12,13}

The Herbal Directive of 2004 contains agreed terminology specific to herbal substances, preparations and herbal medicines, as part of the EU harmonisation process. Table 1 outlines the terminology which applies to herbal products in the EU.

Table 1: EU terminology for herbal products^{8,10,11}

EU TERMINOLOGY
Herbal substance: This refers to mainly dried whole, fragmented or cut plants or parts of plants (flowers, roots etc.) but can include lichen, fungi or algae; fresh material can also be used
Herbal preparation: This refers to preparations/extracts obtained by subjecting herbal substances to certain treatments: for example treatment with a solvent (such as water or more usually ethanol or methanol mixed with water (hydroalcoholic)) to give tinctures, liquid extracts or dry extracts (where the solvent has been removed by evaporation to give a more concentrated extract). Herbal preparations can also be made by distilling the herbal substance to recover what is called the “essential” or volatile oil e.g. Peppermint Oil, Eucalyptus Oil or Tea Tree Oil
Herbal medicinal product: This refers to any medicinal product exclusively containing as active ingredients one or more herbal substance, or one or more herbal preparation
Traditional Herbal Medicinal Product (THMP): This describes a herbal medicinal product that fulfils certain criteria in terms of indications, route of administration and length of usage in clinical practice
Community herbal monograph: This describes a document whose purpose is to provide a scientific summary of all data available on the safety and efficacy of a herbal substance / preparation intended for medicinal use

Not all herbal products in the EU are marketed as medicines. **Herbal products may be classified and marketed as food** provided that they (1) fall outside the legal definition of a medicinal product and (2) comply with the applicable EU food legislation (i.e. they are marketed in the form of food supplements and comply with rules on nutrition and health claims allowable for foods).^{14,15}

APPROVAL PROCEDURES FOR HERBAL MEDICINES

Prior to the implementation of the EU Herbal Directive, all medicines (including herbal medicines) were required to fulfil the same scientific requirements for quality, clinical efficacy and safety as conventional medicines in order to achieve a **marketing authorisation (MA)** within the EU, although as previously noted, not all herbal medicines would have been able to do so.^{7,9} The MA procedure is still available for herbal medicines; however in addition, a simplified **traditional-use registration** system has been introduced for those herbal medicines that fulfil specific requirements related to “traditional use”.^{9,16} Of note, **herbal medicine approval procedures remain under national regulatory control**, under the terms of the Herbal Directive.^{7,9}

Traditional-Use Registration System

The traditional-use registration (TUR) system permits a herbal medicine, which has confirmed traditional use, to be registered nationally as a **traditional herbal medicinal product (THMP)**.^{8,17} The aim is to provide a simplified approval procedure for such herbal medicines, while ensuring satisfactory quality, safety and efficacy, in the interest of public health.^{7,9} The criteria by which “traditional use” is determined for a herbal medicine are outlined in Table 2.

Table 2: Requirements for a traditional-use herbal medicine (THMP)^{7,9,17}

It must be intended and designed for use <i>without</i> the supervision of a medical practitioner for diagnosis, prescription or monitoring of treatment (indications appropriate to traditional usage)
It must be administered in accordance with a specified strength and dosage regimen
It must be an oral, external and/or inhalation preparation
It must provide evidence of medicinal usage throughout a period of at least 30 years (at least 15 years of such usage in EU) of the herbal product or a corresponding herbal product (“long-standing use”)
It must provide sufficient evidence to support (1) traditional medicinal usage (including evidence to support plausibility for efficacy) and (2) safety within the specified conditions of proposed usage

In order for a herbal medicine to qualify for traditional use, sufficient data to support the pharmacological plausibility for the specific preparation in the proposed therapeutic indication must be supplied.¹⁷ In addition, **full information on the quality aspects of the specific herbal product must also be provided by the company**.^{18,19}

Marketing Authorisation Procedure

Not all herbal medicines are eligible for the TUR scheme. Those ineligible for TUR include (a) newly-developed herbal medicines (b) those for which sufficient data cannot be obtained (e.g. cinnamomi camphorae)²⁰ or (c) those which cannot fulfil the specific criteria, listed in Table 2 for TUR (e.g. medical supervision is recommended for black cohosh;²¹ rauwolfia is designated as a “prescription only medicine”;²² there is a lack of pharmacological plausibility for a urethritis indication for ispaghula husk²³). These herbal medicines may only be approved via the conventional MA route (and fulfil requirements for quality, safety and clinical efficacy data, appropriate to the active herbal ingredient and the proposed therapeutic use).^{7,16}

Well-established use: Under EU legislation, the concept of “well-established use” is available for any

medicine (i.e. those derived from chemical, biological and herbal sources).¹⁶ **This requires provision of sufficient publicly available scientific data, to demonstrate that the product in question has been used extensively in clinical practice** (for the specific therapeutic indication under review) typically for at least 10 years in the EU.^{8,16} If well-established use can be proven for any medicine (including herbal medicines), based on published scientific literature, no additional pre-clinical or clinical studies may be required to support national approval (MA) for that medicine. It should be noted however, that any herbal product wishing to use the well-established use route, must always supply evidence to support the quality of that product.^{17,18}

Full / stand-alone marketing authorisation procedure: For herbal medicines that do not fulfil the criteria for either the TUR scheme or marketing authorisation based on well-established use, an approval can only be achieved by way of provision of full scientific data on clinical efficacy and safety (from clinical trials), as well as satisfactory non-clinical safety and quality data.^{8,16}

EU HARMONISATION OF HERBAL MEDICINES

A main aspect of the Herbal Directive was the introduction of a procedure for harmonisation of information for herbal substances and preparations by the development of agreed “monographs”.^{7,24} As part of this legislation, a specific scientific committee (the Herbal Medicinal Products Committee) was established, comprising herbal experts from all EU member states who facilitate the harmonisation procedures.^{10,24}

Herbal Monographs

A core task for the Herbal Medicinal Products Committee (herbal committee) is to establish harmonised (known as community) “monographs” for traditional and / or well-established use herbal medicines.²⁵ **The monograph template is similar to that of the Summary of Product Characteristics** used for conventional medicines; it provides information on agreed uses of the herbal product, the intended patient group, dosage regimens appropriate to the herbal product as well as safety information (undesirable effects and interactions with other medicines).^{24,26}

When preparing a community herbal monograph, the herbal committee undertakes a scientific review of all available data (non-clinical and clinical) for the herbal medicine as well as documented evidence to support either traditional or well-established use.²⁴ It should be noted that some herbal products may have dual well-established use / traditional-use community monographs, depending on the extract type and/or therapeutic indication (e.g. linseed and saw palmetto).^{27,28}

The final agreed version of the community monograph is published, together with an assessment report and list of references (used during the development of the monograph) on the website of the European Medicines Agency.^{24,26} The herbal committee publishes regular updates on the number of herbal substances it has reviewed as part of the monograph development process; it also issues public statements when it has not been possible to establish a community monograph for a herbal substance (e.g. mistletoe).^{29,30} **Published monographs are a useful online resource for healthcare professionals**, and they may also be used as reference documents by companies / national regulatory authorities during an approval procedure for a herbal medicine.²⁴ There are more than 160 community monographs to date and these are accessible online through the EMA website as follows: access www.ema.europa.eu, click on “Find a Medicine”, then “Herbal Medicines” and follow the instructions.²⁴

The Herbal Directive has also established an “**EU list of herbal substances, preparations and combinations thereof**” for use in the TUR system.¹⁹ The list includes the following information: therapeutic indication, specified strength, dose, route of administration and any relevant safety information relating to the herbal substance/preparation. This information is legally binding on companies and member states in terms of safety data and clinical usage claims for those herbal medicines included on the list.¹⁹ However, although there are more than 160 community monographs, very few herbal substances have been entered on this EU list to date.^{19,26} Moreover, a specific herbal medicinal product does not need to be entered onto the EU list in order to qualify for the TUR scheme, once it can fulfil the criteria laid down in Table 2 and full data in relation to its quality are provided.^{16,18,31}

HERBAL MEDICINES IN IRELAND

In Ireland, the Health Products Regulatory Authority (HPRA) is the designated competent authority for implementing the provisions of the Herbal Directive.¹⁷ Therefore both the **traditional-use registration** and **conventional marketing authorisation systems** (either (a) well-established use or (b) provision of a full dossier of clinical and non-clinical studies to support clinical efficacy and safety) are available for herbal medicine approval in Ireland.

The HPRA has established an expert herbal sub-committee to assist in the implementation of the new herbal approval systems.^{17,18} Table 3 outlines some of herbal substances / preparations registered as THMPs to date in Ireland. The full list of registered THMPs, together with the Summary of Product

Characteristics, a detailed public assessment report and a patient information leaflet for each THMP is publicly available on the HPRA website (www.hpra.ie/homepage/medicines/medicines-information/herbal-medicines-list).

Table 3: Some of the herbal substances registered as THMPs in Ireland*

Herbal Substance / preparation	Approved Indication(s) as Traditional Herbal Medicinal Product*
Tincture from agnus castus fruits	A traditional herbal medicinal product for the relief of minor symptoms of premenstrual syndrome, exclusively based upon long-standing use.
Arnica montana L.s.l. (fresh arnica flowers)	A traditional herbal medicinal product for the symptomatic relief of muscular aches, pains and stiffness, sprains, bruises and swelling after contusions, exclusively based on long-standing use.
Devil's claw root	A traditional herbal medicinal product for the relief of minor joint pain in adults, exclusively based upon long-standing use.
Echinacea purpurea	A traditional herbal medicinal product used to relieve common cold and flu-like symptoms in adolescents and adults, exclusively based on long-standing use.
Ginkgo biloba	A traditional herbal medicinal product used to alleviate age-related memory loss and alleviate the symptoms of poor blood flow in conditions such as cold hands and feet. This is exclusively based on long-standing use. Prior to treatment other serious conditions should have been ruled out by a medical doctor.
Saw palmetto fruit	A traditional herbal medicinal product used for the relief of lower urinary tract symptoms in men who have a confirmed diagnosis of benign prostatic hypertrophy (BPH), exclusively based on long-standing use. Prior to treatment other serious conditions should have been ruled out by a medical doctor.
Valerian (tincture and powder preparations)/ Humulus (tincture)	A traditional herbal medicinal product to aid sleep / for the relief of symptoms of mild mental stress, exclusively based on long-standing use.

* Full listing of registered THMPs is available at: www.hpra.ie/homepage/medicines/medicines-information/herbal-medicines-list

One of the requirements of eligibility for TUR is that the herbal medicine should be used without medical supervision, therefore there is a requirement for some of the registered THMPs that they should only be used once serious conditions have been ruled out by a medical doctor (e.g. saw palmetto fruit and ginkgo – see Table 3).³²

In Ireland, herbal products registered as **THMPs are allocated a TR number** which should be visible on the packaging and patient leaflet.^{10,32}

Herbal medicines, approved via either of the conventional marketing authorisation routes, are included on the conventional human medicines listing (search via the “find a medicine” facility on the homepage of the HPRA www.hpra.ie). These medicines are allocated a standard **PA number** which should be visible on the packaging and patient leaflet, e.g. Arkovox® syrup (containing ivy leaf).^{10,33}

Adverse Reactions: As with all medicines, reporting suspected adverse reactions of approved herbal medicines (irrespective of the route of approval) is important to enable continued monitoring of the benefit/risk balance of these products. Healthcare professionals (and consumers) can report any suspected adverse reaction / quality defect with a herbal medicine to the HPRA pharmacovigilance unit (either by using the online reporting system at: <http://www.hpra.ie/homepage/about-us/report-an-issue>; or by email to: medsafety@hpra.ie)

Additional Sources of Information on Herbal Medicines³⁴⁻³⁶

www.hpra.ie/homepage/medicines/regulatory-information/medicines-authorisation/herbal-medicines.

HPRA website containing helpful information on herbal medicines for consumers and companies in Ireland.

www.ema.europa.eu. EMA website containing the list of herbal substances that have community monographs or are currently under review (click on human regulatory / herbal products).

http://ec.europa.eu/health/human-use/herbal-medicines/index_en.htm. Website providing general information on the herbal medicines in the EU including the EU “list of herbal substances, preparations and combinations thereof” for use in the traditional-use registration scheme.

www.ema.europa.eu/docs/en_GB/document_library/Report/2011/05/WC500106706.pdf. Information on the implementation of provisions of the Herbal Directive, according to member state.

The **National Medicines Information Centre** clinical enquiry answering service has access to several data sources in relation to herbal preparations and is happy to address specific herbal medicine-related queries from healthcare professionals. Contact us at: **01 4730589** or email us at: nmic@stjames.ie

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List of references available on request. Date of preparation: March 2016

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug.

HERBAL MEDICINES: REFERENCES

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