IPAR

Public Assessment Report for a
Traditional Herbal Medicinal Product
for Human Use

TR Holder

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I. INTRODUCTION

Specific provisions were introduced for traditional herbal medicinal products (THMPs) in accordance with the Traditional Herbal Medicinal Products Directive (2004/24/EC). The national regulations, the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. No. 540 of 2007) which implement this Directive came into force on 23rd July 2007. Consequently the HPRA has established the Traditional Herbal Medicinal Products Registration Scheme.

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a Certificate of Traditional Use Registration for a specific traditional herbal medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of EC Directive 2001/83/EC, as amended by Directive 2004/27/EC and Directive 2004/24/EC. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the traditional herbal medicinal product for marketing in Ireland.

Based on the review of the data on quality, safety and traditional use, the HPRA has granted Holland & Barrett International Limited a Certificate of Traditional Use Registration for Holland and Barrett Hypericum Hard Capsules, containing St John's wort Dry Extract.

This application was submitted as a standard application according to Article 16a 1 of Directive 2001/83/EC, as amended, as part of the Traditional Herbal Medicinal Product Registration Scheme.

The Summary of Product Characteristics (SmPC) for this traditional herbal medicinal product is available on the HPRA's website.

II. QUALITY ASPECTS

This application is for Holland and Barrett Hypericum Hard Capsules. The active ingredient of Holland and Barrett Hypericum Hard Capsules is an extract obtained from St. John's Wort plant (*Hypericum perforatum* L.).

II.1 S.1 Herbal Substance

The herbal substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.2 S.2 Herbal preparation

The herbal preparation is St John's Wort Quantified Dry Extract, described in the European Pharmacopoeia, and is manufactured in accordance with the principles of good manufacturing practice (GMP).

The herbal preparation specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The composition of the medicinal product is stated in sections 2 and 6.1 of the SmPC. A description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of GMP at suitably qualified manufacturing sites.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for hard capsules, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging material complies with EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Conclusion on quality

The important quality characteristics of the product are well-defined and controlled. Satisfactory pharmaceutical documentation has been provided, assuring consistent quality of Holland and Barrett Hypericum Hard Capsules.

III. NON-CLINICAL ASPECTS

Holland and Barrett Hypericum Hard Capsules is a traditional herbal medicinal product as defined by Article 16a(1) of Directive 2001/83/EC, as amended.
The HPRA has been assured that GLP standards were followed in an appropriate manner in the studies conducted.
An expert report on safety has been provided which includes an appropriate review of the available literature. Overall, the information presented demonstrating traditional use is considered to be acceptable and the lack of provision of a complete standard safety package is in line with the EMA 'Guideline on Non-clinical Documentation for Herbal Medicinal Products in Applications for Marketing Authorisation (bibliographical and mixed applications) and in Applications for Simplified Registration' (EMEA/HMPC/32116/05).

In a genotoxicity test performed, weak positive results of an ethanolic extract in the AMES-test (salmonella typhimurium TA 98 and TA 100, with and without metabolic activation) were assigned to quercetin and are irrelevant to human safety. No signs of mutagenicity have been detected in further in vitro and in vivo test systems.
An environmental risk assessment is not required for herbal medicinal products according to guidance CPMP/SWP/4447/00.

IV. CLINICAL ASPECTS

This is a national application submitted by Holland & Barrett International Limited under Article 16a 1 of Directive 2001/83/EC, as amended.

Holland & Barrett Hypericum Hard Capsules is a traditional herbal medicinal product used to relieve the symptoms of slightly low mood in adults, exclusively based upon long-standing use.

IV.1 Clinical Efficacy

There is no requirement under the Traditional Herbal Registration Scheme to prove scientifically that the product is efficacious, the registration is based exclusively upon the longstanding use of Holland & Barrett Hypericum Hard Capsules as a traditional herbal medicine and not upon data generated from clinical trials.

Article 16c1(c) of Directive 2001/83/EC requires the applicant to provide bibliographic or expert evidence to show that the medicinal product in question, or a corresponding product, has been in medicinal use throughout a period of at least 30 years, including at least 15 years within the Community. With regard to this traditional use data, the requirements of Article 16c1(c) have been met.

The efficacy of this traditional herbal medicinal product is plausible on the basis of long standing use and experience.

The indication proposed for Holland & Barrett Hypericum Hard Capsules is in line with traditional indications recorded and hence, compatible with the requirements of the Traditional Herbal Medicinal Products Directive (2004/24/EC).

IV.2 Clinical Safety

In accordance with Article 16c1(d) the applicant has provided a bibliographic review of the safety data together with an expert report.

This product is for use in adults and older people only. It should not be used in children and adolescents aged 18 years or younger as adequate data are lacking and medical advice should be sought.

This product is intended for the relief of symptoms of slightly low mood. Patients with symptoms and signs of depression should consult a doctor for appropriate treatment. Symptoms of depression include low mood, feelings of helplessness and hopelessness, loss of interest in daily activities, changes in appetite or weight, changes in sleeping patterns, loss of energy, difficulty in concentrating and thoughts of self harm or suicide.

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

If symptoms worsen during use or persist after 4 weeks of using this product, a doctor or pharmacist should be consulted. Patients should consult their doctor urgently if they feel agitated, restless or have thoughts of harming themselves or of suicide.

Patients should consult their doctor before using St John's wort if they have previously been diagnosed with a psychiatric illness or are on any medicines for psychiatric illness. St John's wort should be used with caution in patients with a history of bipolar disorder (also known as manic depression), mania or hypomania.

St John's wort has been shown to induce the cytochrome P450 enzymes CYP1A2, CYP2C9, CYP2C19, CYP3A4 as well as the transport protein, P-glycoprotein. This results in pharmacokinetic interactions with a large number of medicines. Therefore the concomitant use of certain medicines in contraindicated. Examples of such medicines are outlined in section 4.5 of the Summary of Product Characteristics.

Special care should also be taken with the concomitant use of certain other medicines. This includes all drug substances whose metabolism is influenced by CYP1A2, CYP2C9, CYP2C19, CYP3A4 or p-glycoprotein because a reduction in plasma concentration of these drug substances is possible.

St John's wort interacts with hormonal contraceptives. This interaction reduces the effectiveness of these contraceptives and increases the risk of unplanned pregnancy. Intracyclic menstrual bleeding may also occur. This applies to all hormonal contraceptives i.e. the oral contraceptive pill, emergency contraceptive pill, hormonal implants, injections or patches. Women using hormonal contraceptives for pregnancy prevention should use additional contraceptive measures. There are currently no data on interactions with hormone-releasing intrauterine devices but this warning should also be taken into consideration when using hormone-releasing intrauterine devices. There is inadequate data available on the potential effects of St John's wort on fertility.

Patients who have undergone transplant surgery and are taking immunosuppressant medicines should not take St John's wort because of the risk of transplant rejection due to immunosuppressant failure through CYP450 induction.

Clinically significant pharmacodynamic interactions have also been identified with the SSRI antidepressants and the triptan group of medicines used to treat migraine. Due to the increased risk of undesirable serotonergic effects associated with these interactions, St John's wort should not be used concomitantly with these types of medicines.

The safety of St John's wort during pregnancy and lactation has not been established. Animal studies have shown equivocal results with regard to reproductive toxicity, with some data suggesting that hypericin (one of the constituents of St John's wort) may have teratogenic effects. In the absence of sufficient data, use of St John's wort during pregnancy and lactation should be avoided.

St John's wort should not be used in patients with known dermal photosensitivity, those undergoing phototherapy or any photodiagnostic procedures or during intense ultraviolet (UV) exposure. In fair-skinned individuals, sunburn type reactions may occur on skin areas exposed to strong sunlight due to photosensitisation by St John's wort. Patients taking this product should avoid excessive sunbathing or the use of sunbeds or solariums.

St John's wort should be discontinued 10 days prior to elective surgery due to the potential for St John's wort to interact with drugs used during general and regional anaesthesia. Based on the data available for CYP3A, the raised enzyme activity can be expected to return to normal within one week of stopping St John's wort.

Adequate studies on the effects on the ability to drive and use machines have not been performed. In rare cases, St John's wort may cause dizziness or drowsiness. If affected, patients should not drive or operate machinery.

St John's wort is recognised to cause side effects in certain users. Side effects which have been reported include indigestion, poor appetite, nausea, diarrhoea, constipation, tiredness, restlessness and sunburn-like reactions on skin exposed to strong sunlight or strong ultraviolet (UV) light E.g. sun beds. Other side effects that have been reported include headaches, nerve pain or tingling, anxiety, dizziness, over-activity, racing thoughts and decreased need for sleep.

One case of overdose with St John's wort has been published in the medical literature. The patient ingested 4.5 g St John's wort dry extract per day for two weeks followed by an additional 15 g St John's wort dry extract just before hospitalisation. It was reported that the patient experienced seizures and confusion.

When a large overdose of St John's wort has occurred, phototoxic skin reactions may occur. The skin of the patient should be protected from UV irradiation and sunlight for 1-2 weeks. Outdoor activities should be restricted and clothes and/or sun block preparations used to protect the skin from sunlight.

Not all St John's wort products are prepared in the same way. This may affect the composition (E.g. hyperforin and hypericin contents) and consequently the efficacy and safety profile of different St John's wort products. This should be taken into account when changing between St John's wort products.

In conclusion, this product proves not to be harmful in the specified conditions of use based on the review of safety data, expert report and additional data provided.

IV.3 Pharmacovigilance

It should be noted that in accordance with Article 16g of Directive 2001/83/EC, as amended, the pharmacovigilance requirements described in Articles 101- 108 of Directive 2001/83/EC, as amended, also apply in respect of traditional herbal medicinal products.

V. OVERALL CONCLUSIONS

The important quality characteristics of the product are well-defined and controlled. Satisfactory pharmaceutical documentation has been provided, assuring consistent quality of Holland & Barrett Hypericum Hard Capsules.

The HPRA, on the basis of the data submitted, considered that Holland & Barrett Hypericum Hard Capsules demonstrated adequate evidence of traditional use for the approved indication and no new preclinical or clinical safety concerns have been identified.

A certificate of traditional use registration for Holland & Barrett Hypericum Hard Capsules is granted.

VI. REVISION DATE

February 2021

VII. UPDATES

Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/non approval
CRN00C3G0 TR Transfer	SPC section 7, 8 Package Leaflet New TR Holder: Holland & Barrett Limited, Cedar Drive, Dublin Airport Logistics Park, Saint Margarets, Co Dublin, K67 E0C5, Ireland New TR number: TR23157/003/001	26/02/2021	26/02/2021	Approved