CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Tempocol, 182 mg gastro-resistant capsule, soft
Will Pharma B.V., the Netherlands

Mentha piperitae aetheroleum

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2376/001/DC
Registration number in the Netherlands: RVG 109856

2 April 2013

Pharmacotherapeutic group:	other drugs for functional bowel disorders
ATC code:	AO3AX
Route of administration:	oral
Therapeutic indication:	herbal medicinal product for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain
Prescription status:	non prescription
Date of authorisation in NL:	23 November 2012
Concerned Member States:	Decentralised procedure with BE, LU
Application type/legal basis:	Directive 2001/83/EC, Article 10a

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Tempocol, 182 mg gastro-resistant capsule, soft from Will Pharma B.V. The date of authorisation was on 23 November 2012 in the Netherlands.

This herbal medicinal product is indicated for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain.
Tempocol is indicated in adults, adolescents and children aged 8 to 12 years

A comprehensive description of the indications and posology is given in the SPC.

The principal pharmacodynamic effect of peppermint oil relevant to the gastrointestinal tract is a dose-related antispasmodic effect on the smooth musculature, due to the interference of menthol with the movement of calcium across the cell membrane.
Peppermint oil showed antifoaming and carminative activity *in vitro*. Reductions in gastric and intestinal foam volume were observed in *in vitro* studies with peppermint oil.

The enteric coating delays the release of the product until it reaches the distal small bowel, exerting local effects on colon relaxation. The exact mechanism of action is however unclear.

This decentralised procedure concerns gastro-resistant soft capsules containing 182 mg essential oil of peppermint (*Mentha piperitae* aetheroleum). The legal basis for this application is article 10a of Directive 2001/83/EC (well established medicinal use). The well-established use was substantiated by making reference to Colpermin and Medacalm, products on the UK and German market and by reference to the HMPC (Committee on Herbal Medicinal Products) community herbal monograph for well established use of *Mentha x piperita* aetheroleum (EMEA/HMPC/349466/2006).

The marketing authorisation is granted based on article 10a of Directive 2001/83/EC.

This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ''Medicinal use'' does not exclusively mean ''use as an authorised medicinal product'', so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

No scientific advice has been given to the MAH with respect to these products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is peppermint oil (*Mentha piperitae* aetheroleum), an established substance described in the European Pharmacopoeia (Ph.Eur.*). Peppermint oil is the essential oil obtained from fresh aerial, flowering parts of *Mentha x Piperita* L. It is a colorless, pale yellow or pale greenish-yellow liquid. A "crude" peppermint oil is used as starting material for the manufacturing of the active pharmaceutical ingredient, peppermint oil. Full data on the synthesis were provided.

Manufacturing process
The MAH has provided information on the production of the crude oil. The crude *Mentha piperita* oil is refined to the active ingredient. Process validation data have been provided on three batches.

Quality control of drug substance
Specifications of both "crude" and "refined" peppermint oil are in compliance with Ph. Eur monograph. Pharmacopoeial specifications are supplemented with additional limits. Limits set for pesticides are in accordance with the Ph. Eur. This considered acceptable because it is confirmed that only pesticides covered by the Ph.Eur. are used in the production of the starting material. Batch analytical data from three production-scale batches were provided. The batches complied with the proposed specification and are acceptable.

Stability of drug substance
Stability studies have been performed with the drug substance during storage at 25°C ± 2°C/60% RH, 30°C ± 2°C/65% RH and at 40°C ± 2°C/75% RH. No significant changes in any of the parameters were observed. The proposed retest period of 12 months is justified.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Tempocol 182 mg contains 182 mg of *Mentha piperitae* aetheroleum (peppermint oil). It is an oval shaped, transparent-opaque soft capsule containing a clear liquid.

The gastro-resistant soft capsules are packed in blister packs.

The excipients are: gelatin, glycerol, ethylcellulose, sodiumalginate (E401), medium-chain triglycerides, oleic acid.

Pharmaceutical development
The development of the drug product was conducted to obtain a soft capsule containing 182 mg of the drug substance in the smallest possible capsule size. An adequate description of the choice of the materials was presented. The drug substance is the single component of the fill because its viscosity allows encapsulating it without any diluents. Excipients used in the formulation of the drug product - gelatin, glycerol and water - are typical components of soft capsule shells. Gelatin is the main component of a shell. The capsules are enteric coated in order to release the drug substance in an intestine and to

avoid irritations of the gastric mucosa. The enteric coating consists of two ingredients: ethylcellulose and sodium alginate. Both are widely used in oral preparations. The materials provide an enteric coating of the capsules that fulfils the requirements of Eur. Ph. on enteric coated capsules. The development of the drug product has been described in sufficient detail.

Manufacturing process
The filling and forming of the capsules is performed in a one step operation. A flow diagram is presented giving the steps of the process and showing where materials enter the process. The points where in-process controls are conducted are identified. All are considered to be acceptable.
For the fill weight a variation of ± 5% is used. This variation is considered acceptable because it is in line with the release specifications of ± 5% for the peppermint oil content. Peppermint oil is the only constituent of the fill. The other controls are considered to be adequate for the process.
The process validation of the manufacturing process of peppermint oil capsules was carried out with three consecutively produced pilot batches. Validation included appropriate parameters.

Control of excipients
The capsule shells are produced with pharmacopoeial excipients; glycerol 99.5%, purified water and gelatin. All comply with the Ph.Eur. For the coating two non-pharmacopoeial excipients are used Surelease E-7-19040 and NS Enteric 29Z19241. Both consist of different ingredients, which are all described in pharmacopoeias.

Quality control of drug product
The product specifications cover appropriate parameters for this dosage form. Except for appearance and content, all methods used are in accordance with the Ph.Eur. For identity the method, profile and limits of the Ph.Eur. monograph on peppermint oil are used. The content is determined by an in house method. The assay has been adequately validated with respect to precision, selectivity, accuracy, linearity and robustness. The proposed limits for the content of the active compound at the end of shelf life, are in line with herbal guidelines.
Batch data of 3 production batches were provided. The batch analysis results show that the finished products meet the specifications proposed.

Stability of drug product
Stability studies were conducted with three industrial-scale production batches during storage at 25°C/60% RH, 30°C/65% RH and 40°C/75 % RH. Stability data for up to 12 months are presented. All parameters tested remained within specification under all conditions tested. Based on the submitted data and the Guideline on stability testing the claimed shelf life of 12 months can be granted. In accordance with the guideline on the declaration of storage conditions, a storage statement is not required.
The stability studies initiated are continued. Data will be submitted in due time. This is noted as a commitment.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Gelatin is the only excipient from animal origin. A CEP of gelatine as well as a certificate with respect to the TSE/BSE safety is included. This is acceptable.

II.2 Non-clinical aspects

This product is a well-established formulation which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.
Overall, it is concluded that based on the non-clinical data, Tempocol could be expected to exert a large number of actions. Specifically it is noted that based on the non-clinical dossier, at least potential toxicity at the maximum recommended dose (compared to the ADI for menthol of 4 mg/kg/day and compared to reported human lethal effects at 50-500 mg/kg), and that potential pharmacodynamic (in particular with

calcium blockers) and pharmacokinetic interactions (P450 enzymes, conjugation, absorption enhancing effect) exist.
Other theoretically relevant effects could be cardiovascular effects, effects on central and peripheral nervous system, effects on intestinal flora, hepatotoxicity, immunomodulatory effects, local (intestinal) irritation.

Environmental risk assessment
No risk management plan was submitted. Reference is made to the documents EMA/HMPC/71049/2007 and EMA/CHMP/SWP/4447/00, in which it is stated that herbal medicinal products are exempted because they are unlikely to result in significant risk to the environment due to the nature of their constituents. This rationale is acceptable.

II.3 Clinical aspects

Pharmacokinetics
There are no studies performed with the current formulation. As menthol and other cyclical mono-terpenes in the peppermint oil are highly fat-soluble they are rapidly absorbed from the proximal small intestine when taken orally. Enteric-coated capsules resist degradation and release of the oil in the stomach. After oral administration of an enteric coated formulation, maximal menthol concentrations of about 3 hours are observed in healthy subjects.
The capsule submitted for marketing authorisation is a gastro-resistant capsule. In vitro dissolution data supports the gastro-resistance of the formulation, which is considered sufficient support for this application. Terminal half-life (t1/2) for menthol is about 3.7 h.

There are no specific data on the pharmacokinetics of single constituents after administration of peppermint oil to subjects in special groups such as patients with hepatic or renal failure, aged patients or children.

In the HMPC Community monograph on *Mentha x piperita* L. aetheroleum it is stated that the use of food or antacids administered at the same time could cause early release of capsule content. Other medicinal products used to decrease stomach acid, like histamine-2 blockers and proton pump inhibitors may cause premature dissolution of the enteric coating and should be avoided.
Antacids should not be administered at the same time as oral preparations of peppermint oil.
Based upon the provided data, at the recommended dose, a interaction with felodipine is not expected.
Possible interaction of menthol cough drops with warfarin were described in two case reports. Possible interaction was observed in 57-year-old white male awaiting cardioversion for atrial fibrillation prescribed warfarin.

<u>Effects on CYP 450 enzymes</u>
Although peppermint has been observed to inhibit cytochrome P450 isoenzyme 3A4 and has calcium channel blocking effects, there are no reports of clinically relevant drug interactions with peppermint oil. In a study in human liver microsomes it was found that peppermint oil and two of its components were moderately effective, reversible, and partially mixed inhibitors of nifedipine metabolism, which is mediated by the cytochrome P450 isoform CYP34A. However, since the dose of peppermint oil in the clinical pharmacology part of the study was about 2-8 times higher than recommended by the monographs (ESCOP 2003, WHO 2002), the results may be not relevant for peppermint leaves or drugs containing a low dose of peppermint oil. An inhibition of CYP3A4 and possible calcium blocking effects cannot be ruled out. The SPC therefore includes that based upon in vitro data, peppermint oil may inhibit CYP3A4 and has calcium channel blocking effects and that an effect in vivo cannot be ruled.

Pharmacodynamics
The principal pharmacodynamic effect of peppermint oil relevant to the gastrointestinal tract is a dose-related antispasmodic effect on the smooth musculature as demonstrated in *in vitro* studies. Menthol, the major constituent of peppermint oil, has properties similar to those of calcium-channel blockers on smooth muscle such as that in the human gut.

Peppermint oil is assumed to act locally. The antispasmodic activity is supported by several human studies. In addition, there is evidence that patients with IBS have a heightened baseline and postprandial contractility, especially in diarrhea-predominant IBS, which may contribute to symptoms like abdominal pain and altered stool frequency. Reduction of colonic contraction and transit time by peppermint oil might improve symptoms like pain and stool frequency. The exact mechanism of action is, however, unknown.

Clinical efficacy

The following indication was applied for: *Symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain, especially in patients with irritable bowel syndrome*. The MAH submitted bibliographical data on 867 IBS patients included in 17 clinical studies from 1980 up to the year 2010. Most were placebo-controlled studies and 300-400 of the patients received peppermint oil.

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder in which abdominal discomfort or pain is associated with defecation or a change in bowel habit, and with features of disordered defecation. Management of IBS in patients is determined by the predominant symptoms, and includes non-pharmacological and pharmacological therapies. Current pharmacological therapeutic options are limited and the effectiveness of many is poorly documented. No single treatment is currently regarded throughout the world as being universally applicable to the management of all IBS patients.

The principal pharmacodynamic effect of peppermint oil relevant to the gastrointestinal tract is a dose-related antispasmodic effect on the smooth musculature as demonstrated in *in vitro* studies. The rationale for the using antispasmodic agents is to attenuate the heightened baseline and postprandial contractility seen in patients with IBS (particularly when diarrhea predominant). The exact mechanism of action is however unknown.

Well-established use

Peppermint oil has been used for generations as a digestive and carminative, also in patients with IBS. Several medicinal products (*e.g.* Colpermin in the UK, Medacalm in Germany) are available within the EU for the relief of symptoms of IBS. The question remains whether the patient population treated historically is representative of the patient population currently defined as having IBS, given that symptoms are not specific and largely overlap with other gastrointestinal conditions.

The MAH submitted bibliographical data on 867 IBS patients included in 17 clinical studies from 1980 up to the year 2010. Most were placebo-controlled studies and 300-400 of the patients received peppermint oil. No other data in the form of epidemiological studies and post-marketing experience with other products containing the same constituents have been provided to support well-established use outside its use in clinical trials. Also, the estimated number of patients with IBS included in clinical trials over 30 years and treated with peppermint oil (300-400) is considered too limited to justify extensive clinical use given the estimated prevalence of IBS of 10-15% in the western population. Therefore, the active substance of Tempocol (peppermint oil) can be considered to have a well established use in the generally claimed indication for symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain, but the inclusion of IBS patients is not acceptable.

Benefits

The majority of the trials in patients with IBS was performed before 1990 and included small cross-over trials including 20-40 patients with a duration of treatment of 2-4 weeks. The results of these earlier trials suggest that peppermint oil may improve IBS symptoms compared to placebo; however, the limited data presented within these publications do no allow proper efficacy assessment in the claimed indication.

Four more recently published randomized placebo-controlled studies allowed more in depth assessment of efficacy based on publication type. Although different outcome measurements were used, all studies reported statistically significant improvement of individual or overall symptoms upon treatment with peppermint oil compared to placebo. Liu et al. (1997) reported that 73%-83% of the patients treated with peppermint oil showed mild to moderate improvement of individual IBS symptoms compared to 23%-43% with placebo after 4 weeks of treatment at a dose of one capsule tid or qid (n_{total}=101). Capanni et al. (2005) showed that treatment with peppermint oil (two capsules tid) significantly increased overall quality

of life score after 3 months of treatment in IBS patients (n_{total}=178); 80% with peppermint oil compared to 36% with placebo reported improved quality of life. Capello et al. (2007) showed that that the number of patients (n_{total}=57) with ≥ 50% reduction in mean total IBS symptoms score was 64% after treatment with peppermint oil (two capsules bid for four weeks) compared to 34% after treatment with placebo. Also, a statistically significant reduction for each individual symptom score was shown. Merrat et al. (2010) showed that percentage of patients (n_{total}=60) with no abdominal pain or distension was 42% upon treatment with peppermint oil compared to 22% for placebo at week 8 at a dose of one capsule tid. No effect was seen on other symptoms.
The data support efficacy of peppermint oil for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain, in general.

One study by Kline et al. (1997) in children with IBS between 8 and 17 years (n_{total}=50) showed that treatment with peppermint oil improves overall symptoms and pain, but did not affect other symptoms at a dose of two capsules tid or one capsule tid (weight between 30-45 kg) compared to placebo after two weeks of treatment.

The dose of peppermint oil in the individual studies submitted was in the range of 1 capsule per day to 6 capsules per day, which is in line with the proposed posology. The most frequently used dosage was 3 capsules per day, followed 1-2 capsules per day. Data of the clinical trials suggests a starting dose of 1 capsule up to three times daily and a maximum dose of 6 capsules per day. The applicant is requested to include this information on starting dose and maximum dose.

Uncertainties in benefits
Patients with IBS: First of all concerns remain on the type of population included in the absence of standardized criteria and proper differential diagnosis (Liu et al. 1997). Furthermore, in case standardized criteria were used (Rome II), information on type of IBS regarding the predominant symptoms (like predominant bowel habit) is often not available, except for the study by Capello et al. (2007), where the majority of the patients had diarrhoea-predominant IBS. In addition, the number of patients included in the trials is very limited given the high prevalence of the disease. Therefore, it is currently unknown whether the observed efficacy data could be extrapolated to the broad spectrum of IBS patients including for instance constipation-predominant IBS.
Secondly, the apparent lack of predefined primary endpoints and validated outcome scales hampers the interpretation of the robustness and clinical relevance of the results obtained. The guidance document (CPMP/EWP/785/97) recommends that the patient's global assessment of symptoms and abdominal pain/discomfort should be used as two primary endpoints for which statistically significant and clinically relevant results must be found. Furthermore, measurement of discomfort/pain should use a validated scale. None of the studies appear to meet all of these criteria. Use of validated and easily interpretable outcome measurements is especially of importance given the often intermittent nature of the disease with symptoms that tend to wax and wane and outcomes being based on patient recording only. Peppermint oil appears to improve a wide range of symptoms to a similar extent which would be favorable for a drug in this indication, but also raises questions on the discriminative nature and validity of the outcome measurement used in the absence of validated scales.
Thirdly, no data are available on repeated use as recommended (CPMP/EWP/785/97), given the chronic and intermittent nature of the disease. The applicant does not differentiate between short term intermittent use and long-term continuous use within the proposed indication; given the limited duration of the clinical trials submitted only an indication reflecting short-term use could be approvable, provided efficacy is demonstrated including repeated use.

The data in the paediatric population (8-17 years) is considered too limited to demonstrate recognized efficacy in the paediatric patients with IBS.

Risks
The size of the individual trials in patients with IBS only is limited. Adverse events and their frequencies were provided from a broader population, including clinical trials with patients suffering from IBS, dyspepsia and tension-type headache. Commonly reported adverse events in these studies were heartburn, eructation with peppermint taste, nausea, blurred vision, and anal burning. Heartburn was

reported in 9 clinical studies with an incidence in the range of 0.3-11.1%. Heartburn is related to the release of oil in the upper gastrointestinal tract, which relaxes the lower oesophageal sphincter, facilitating the reflux. Eructation with peppermint taste was reported in 5 clinical trials with an incidence in the range of 1.7-16.7%. Nausea was reported in 4 clinical studies with an incidence in the range of 1-2.2%. Flatulence was reported in 2 clinical trials with an incidence in the range of 1.4-2.2%. Blurred vision was reported in 2 clinical studies with an incidence in the range of 2.1-3.3%. Anal burning was reported in 2 clinical trials with an incidence in the range of 2-4%. Furthermore, the following events were reported in 1 clinical trial: headache (10%), dizziness (5%), increased sweating (14.3%), epiphora (2.7%), vomiting (1%), diarrhoea (0.8%), dry mouth (13.3%) and rash (0.3%). Adverse events summarised within the HMPC Community monograph (EMEA/HMPC/349466/2006)include perianal burning, hypersensitivity, rash, abdominal pain, bradycardia, muscle tremor, and blurred vision.
Menthol is widely used in foods and various other preparations and in general considered to be safe.

Uncertainties in risks

The number of patients with IBS included in clinical trials is limited (estimated 300 patients) given the relatively high prevalence of the disease (about 10-15%). AE data was provided from a broader population, including use of peppermint oil in other indications. It is unclear to what extent data in other indications are of relevance. AE data differentiating studies relevant for the indication of symptomatic relief of gastrointestinal symptoms and studies with other indications is lacking. Also, a discussion on the possible relatedness of the AEs to peppermint oil and their frequencies, also in relationship with comparator groups in these studies, was lacking. Due to the short term duration of the trials, limited information is available on adverse events during longer periods of follow-up (up to 3 months) and during repeated use. There are limited data from clinical trials substantiating safe use in the pediatric population. No post marketing data was submitted on products resembling the formulation to be marketed and in comparable doses. The relevance of safety information derived from peppermint supplements or menthol in foods showing limited adverse events is questioned as lower doses are used and most likely for shorter durations of time.

Discussion on the benefit-risk assessment

Peppermint oil has been used for generations as a digestive and carminative, also in patients with IBS. It is reasonable to assume that the active substance has been extensively used for the relief of gastrointestinal symptoms like spasms and flatulence. The question remains whether the patient population treated historically is representative of the patient population currently defined as having IBS, given that symptoms are not specific and largely overlap with other gastrointestinal conditions.

The lack of adequate bridging data between Tempocol and the products used within the bibliographic data is of concern as peppermint oil is considered to act locally within the gastrointestinal tract and differences in formulation might affect release pattern and local concentrations.
Limited information is documented on the safety of peppermint oil in the target population. Small numbers of patients were included in the trials. AE data from a broader population was provided, including use of peppermint oil in other indications. It is unclear to what extent data in other indications are of relevance. Information on long-term use is limited. Post-marketing data on comparable formulations were not submitted. Overall, albeit based upon limited documented data in a broader population and in the context of short-term use, considering the commonly reported adverse events, and considering the fact that peppermint oil has been used for many years without reports of significant safety issues in man identified in literature, the safety profile of peppermint oil can be accepted. An AE analysis was performed, differentiating studies relevant for the indication of symptomatic relief of gastrointestinal symptoms and studies with other indications. The possible relatedness of the AEs to peppermint oil and their frequencies were included in section 4.8 of the SPC.
As requested by the member states, the MAH deleted the proposed contraindication for special populations with severe liver damage and gall bladder inflammation due to lack of data and referring to the “Public Statement on the Use of Herbal Medicinal Product Containing Pulegone and Menthofuran” (EMEA/HMPC/138386/2005), which does not propose a contraindication but *an alerted pharmaco-vigilance of peppermint oil and mint oil containing products is recommended*. Specific attention to liver toxicity within the PSURs. A warning for use in patients with severe liver damage and gall bladder inflammation was included in section 4.4 of the SPC.

The bibliographic data in support of efficacy in patients with IBS consists of various small trials resulting in a total of 300-400 patients with IBS receiving treatment with enteric-coated peppermint oil. Although most studies showed a favorable effect on relief of symptoms compared to placebo, uncertainties with regard to the target population included, the variability and validity of outcome measurement used, and the lack of data on long-term or repeated use, hampers efficacy assessment. Due to the small number of patients included, the clinical relevance of the obtained treatment difference between peppermint oil and placebo and the population that would benefit most from treatment (given the broad spectrum of symptoms) could not be determined. The data are therefore considered sufficient to support relief of gastrointestinal symptoms in general, but future studies are required to substantiate efficacy in patients with IBS. These studies should include larger number of patients using standardized diagnostic criteria and symptom scales and which are of sufficient duration.

With regard to the IBS indication, the MAH argued that the HMPC monograph should be considered as state of scientific findings which is valid unless new findings might change the state of scientific knowledge. The member states have thoroughly taken into account the HMPC monograph and the underlying data and also the CHMP guidance document relevant for the treatment of IBS ("Points to Consider on the Evaluation of Medicinal Products for the Treatment of Irritable Bowel Syndrome" (CPMP/EWP/785/97)). It is agreed that part of the evidence in support of the indication and submitted has already been assessed within the context of the HMPC monograph. An apparent difference is that within the HMPC monograph reference is also made to the document "Points to Consider on the Evaluation of Medicinal Products for the Treatment of Irritable Bowel Syndrome" (CPMP/EWP/785/97), and that despite identified limitations, the available data is still considered sufficient to conclude that peppermint oil is clinically effective in the treatment of IBS symptoms. A reference is made to several randomized well designed controlled trials which are not specified.
The RMS questioned the inclusion of IBS patients within the indication given the deviations from the points to consider document within the submitted literature, also taking into account new data that have become available after the HMPC monograph was agreed upon (randomized placebo-controlled studies by Capanni 2005, Capello 2007, and Merat 2010). This mainly relates to lack of data meeting current requirements to include a specific reference to patients with IBS.
The uncertainty regarding efficacy in patients with IBS is in fact reflected by the more recently published reviews submitted by the MAH. These reviews also take into account the more recently published trials that were not taking into account in the HMPC monograph. Based on these reviews, it can be concluded that the efficacy of peppermint oil in IBS is currently not considered unequivocal, as four out of ten submitted reviews clearly state that additional data is required to confirm the efficacy of peppermint oil in IBS.

Conclusion
Overall, the conclusion of the assessment that the currently available data is insufficient to support efficacy in the specific IBS population, was maintained throughout the procedure. Hence, only a general indication of "herbal medicinal product for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain" is approvable. This means that the product will be available for IBS patients as well as for a broader patient population only for relief of symptoms as described within the indication.

Risk management plan
The Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MAH agreed to pay specific attention to liver toxicity within the PSURs.

Product information

SPC

The content of the SPC approved during the decentralised procedure is acceptable and has been adapted in accordance with the comments of the member states.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. This test ensured that the questionnaire complied with the protocol and that the leaflet used was appropriate for testing. The subjects recruited comply with the guidance given in the legislation and come from a subset that could use of this medicine at some stage in the future.

The test was performed with 20 subjects with a patient information leaflet and questionnaire which were both in English. Subjects were randomly selected. The composition of the subject population is acceptable as far as age, gender and education are concerned.
The technical readability, comprehensibility of the text, traceability of information and the applicability were investigated with 12 applicability questions and 5 general questions related to the readability and layout. Safety issues were addressed with questions related to the contraindications and drug interactions.
The test comprised of only one round with 20 subjects. This is not fully in line with the QRD guidance. However, because the average score was above 90%, a two-round test is not considered necessary.

According to the QRD guidance a satisfactory outcome is when 90% of the participants are able to find the information requested within the PL, of whom 90% can show they understand it, i.e. each and every question must be answered correctly by at least 81% of the participants.
The first criterion is fulfilled. The average score of the 12 questions is 90.4%. The second criteria is not fulfilled because the score of two questions was below 81%; 50 and 80% respectively.

The lowest score of 50% was for a question related to the time of use of the product. This low score is due to a misinterpretation of the question. Ten participant misunderstood this question and consequently responded with the indication instead of the recommended period of intake.
Because all 10 test subjects that understood gave the correct answer, it can be concluded that the information related to the period of use is adequately presented in the leaflet. Nevertheless, as a precautionary measure the MAH proposed to highlight in the patient leaflet the advice to take the capsules before a meal. This proposal was endorsed.

The majority of the test subjects considered the package leaflet well arranged and written in a comprehensible manner. Font and point size were evaluated as acceptable. None of the subjects had difficulty reading the leaflet. The graphical arrangement of the information can be improved because 5 subjects found the layout unfavourable.

In conclusion, the readability test and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. Furthermore, the questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Despite the fact that the user test and outcome are not fully in line with the QRD guidance, they considered acceptable because deviation of the guidelines are adequately justified.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Tempocol, 182 mg gastro-resistant capsule, soft has a proven chemical-pharmaceutical quality and is a well-established medicinal product in the indication 'symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain'.

The well-established use was substantiated by referring to Colpermin and Medacalm, products on the UK and German market, and the HMPC (Committee on Herbal Medicinal Products) community monograph of *Mentha x piperita* aetheroleum concerning well-established use community monograph of *Mentha x piperita* aetheroleum. Additionally an adequate literature overview was provided.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling include adequate information and are in the agreed templates.

In the Board meetings of 31 May 2012 and 27 September 2012, the addition of the words *especially in patients with irritable bowel syndrome* to the proposed indication was discussed. The Board decided that efficacy is not demonstrated in accordance with the well-established use requirements. The indication should therefore be restricted. In the Board meeting of 22 November 2012 the NL prescription status was discussed. The product was classified as UAD, which means that it can be purchased without prescription, exclusively from pharmacies and drugstores.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for Tempocol 182 mg in the approved indication, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 25 October 2012. Tempocol, 182 mg gastro-resistant capsule, soft was authorised in the Netherlands on 23 November 2012.

The following post-approval commitments have been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to conduct stability studies under both real time and accelerated conditions on the first three industrial-scale marketing batches. The results of the on-going stability studies at least up to the proposed shelf life will be provided as soon as available.

<u>Pharmacovigilance</u>

- The MAH committed to pay specific attention to liver toxicity within the PSURs.

List of abbreviations

AE	Adverse Event
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HMPC	Committee on Herbal Medicinal Products
IBS	Irritable Bowel Syndrome
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached

Literature references

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