COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

SeHCAT 370 kBq hard capsules ([^{75}Se] tauroselcholic acid)

NL/H/5413/001/MR

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This module reflects the scientific discussion for the approval of SeHCAT 370 kBq hard capsules. The procedure was finalised on 26 April 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

[^{75}Se] tauroselcholic acid	Selenium-75 Tauroselcholic acid
ASMF	Active Substance Master File
BA	Bile acid
BAM	Bile acid malabsorption
BAS	Bile acid sequestrants
CDER	Center for Drug Evaluation and Research
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FBD	Functional Bowel Disorders
FDA	Food and Drug Administration
GMP	Good Manufacturing Practices
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MeV	Megaelectron Volt
NPV	Negative predictive value
NOAEL	No observed adverse effect level
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PPV	Positive predictive value
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
µCi	Microcurie (Unit for radioactive decay. 1 Ci is equal to 3.7 x 10^{10} disintegrations per second).

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for SeHCAT 370 kBq hard capsules, from GE Healthcare B.V.

This medicinal product is for diagnostic use only.

[^{75}Se] tauroselcholic acid is used for quantitative measurement of the resorption of bile acids. It can be used as an additional diagnostic test for patients with chronic diarrhoea if bile acid malabsorption is suspected or should be excluded.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

This current product has been approved via a mutual recognition procedure (MRP). The national marketing authorisation for this product (RVG 16191) was granted on 14 November 1996 in the Netherlands. The current MRP authorisation has been granted pursuant to Article 8(3) (Full or full-mixed application) of Directive 2001/83/EC and concerns a full application with a mixed design of own studies and literature. For this, the MAH included own (non-clinical) studies of the initial registration procedure.

The concerned member states (CMS) involved in this procedure were Cyprus, Czechia, Greece, Poland, Portugal, Romania and Slovakia.

SeHCAT 370 kBq hard capsules is a radiopharmaceutical product and should only be received, used and administered by authorised persons and in designated clinical settings that comply with the regulations and/or appropriate licenses of the competent official organisations. The required precautions regarding these matters, have been included in the labelling, package leaflet and SmPC of the product. SeHCAT is an oral immediate release capsule, which contains [^{75}Se] tauroselcholic acid as drug substance. The physical half-life of ^{75}Se is approximately 118 days. [^{75}Se] tauroselcholic acid is a bile acid analogue which shows identical physiological behaviour with naturally occurring bile acid conjugates. The product is intended for use in a clinical test to diagnose bile acid malabsorption. The retention in the body or the loss of this compound into the faeces can be studied using a standard gamma camera. The measurement after 7 days represents the retained fraction of bile acids after around 35 enterohepatic cycles (5 per day). Normal values are above 20%; threshold values of below 15%, below 10% and below 5% represent mild, moderate and severe bile acid malabsorption.

II. QUALITY ASPECTS

II.1 Introduction

[^{75}Se] tauroselcholic acid is supplied as capsules of 370 kBq (10 µCi)/capsule at the activity reference date (max. 6 weeks after production). SeHCAT is a hard capsule size 3, consisting of ivory body and orange cap. Each capsule contains less than 0.1 mg of tauroselcholic acid as

active substance. Selenium-75 has a physical half-life of approximately 118 days and decays by gamma emission with principal energies at 0.136 MeV and 0.265 MeV.

The excipients are:
Contents of the capsule - disodium phosphate dihydrate.
Capsule wall - gelatin, titanium dioxide (E171), quinoline yellow (E104), erythrosine (E127).

The hard capsules are packed as single capsule packs in polystyrene containers and the capsules are held in place with polythene foam pads.

II.2 Drug Substance

The active substance is the gamma-emitter [^{75}Se] SeHCAT ([^{75}Se] tauroselcholic acid) molecule, which is not described in the Ph.Eur. Inactive SeHCAT has the appearance of off-white gum. There is no reason to believe that radioactive SeHCAT would be any different. The active substance is produced as an aqueous solution. The physical half-life of ^{75}Se is approximately 118 days.

Manufacturing process
For this product pre-filled ampules with ^{74}Se enriched selenium are prepared. The targets ampules are then irradiated in a nuclear reactor, where selenium-74 is converted to its isotope selenium-75 by a neutron-gamma (n, γ) reaction. The drug substance solution is prepared through a multi-step synthesis which includes the three main stages synthesis, purification and aliquoting of the bulk drug substance solution. Due to the relatively long half-life of selenium-75 and the absence of any significant long lived radionuclidic impurities, there is no need for immediate processing. The information submitted on impurities, including radionuclidic- and radiochemical impurities and residual solvents, is deemed sufficient. The potential radionuclidic impurities will be formed at an extremely low level and the concomitant formation of stable selenium species, either directly or by decay of impurities, is expected to be equally insignificant in relation to their amounts in the original target material.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of relevant guidelines for radiopharmaceuticals. The target material is examined to ensure the degree of enrichment and that there is an absence of significant impurities. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail. Batch analytical data demonstrating compliance with this specification have been provided for three full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches of the bulk drug substance solution. Based on the data submitted, a shelf-life was granted of 14 weeks when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The active substance is the selenium-75 labelled analogue of the naturally occurring bile acid, homocholic acid. The formulation is a mixture of tauroselcholic [^{75}Se] acid on disodium phosphate dihydrate contained within a gelatin capsule. No overage is applied. Disodium phosphate dihydrate is used as both a capsule filler and as absorber of the active ingredient substance. The capsule shells comply with the relevant European Pharmacopoeia monograph and they contain only European Community approved colouring materials. The capsules used during the initial development have been changed (from manually filled to pre-filled capsules) to comply with new regulations and precautions for radiopharmaceuticals. Therefore, additional dissolutions studies were performed to compare the dissolution of the old and new capsules. The results demonstrated that both capsule types show a similar dissolution behaviour. Furthermore, the selected container closure system for the storage of drug product is adequate for packaging, storage, transportation and commercial use of the drug product.

Manufacturing process

Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines. For this product, pre-filled (with disodium phosphate dihydrate) capsules are used. The manufacturing process consists of dilution of the active bulk solution and filling each capsule by measuring the activity in a calibrated ionisation chamber. The production of the pre-filled capsule is considered part of the manufacture of the finished dosage form and the pre-filled capsules are considered an intermediate product. The components of the pre-filled capsules comply with the Ph.Eur. monograph. The manufacturing of the capsules is in accordance with the Good Manufacturing Practices (GMP) and consists of the four basic steps sieving and mixing, weighing, filling the capsule and packaging and storage. The submitted stability data of this intermediate justify a holding time of 2 years. Release testing is performed for each batch by the manufacturer and internal incoming testing is performed by the MAH. Only the batches that meet the specifications are used.

Control of excipients

The compendial excipients comply with the Ph.Eur. The non-compendial excipients, which are the capsule shell colouring agents, comply with EU regulations. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for total activity, radiochemical identity and purity, radionuclidic identity and purity, disintegration, capsule colour, disodium phosphate dihydrate identity, specific radioactivity and microbiological attributes. Due to the radioactivity of the drug product, the microbiological test is performed on the pre-filled

capsules. Limits in the specification for release and stability are identical. The limits have been justified and are considered appropriate for adequate quality control of the product.

An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the non-compendial analytical methods have been provided.

Batch analytical data from three batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability studies have been performed on three batches of SeHCAT capsules stored at ambient temperature for the entire shelf-life of the product. The stability tests radiochemical purity and disintegration were performed. All results met the specification. Based on the stability data, a shelf-life has been granted of 18 weeks from manufacturing date and 12 weeks from calibration date. The shelf-life included in de SmPC states '*The shelf life for this product is 18 weeks from the date of manufacture. The expiration date for this product is 12 weeks from the activity reference date stated on the label.'* The labelled storage conditions are: *'Store below 25°C. Do not store in the freezer. Store in the original package protected from light. Storage of radiopharmaceuticals must be in accordance with national regulations for radioactive material'.*

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for the excipient gelatin, used in the hard gelatin capsules, have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that SeHCAT has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The MAH submitted a literature review and has not provided additional studies and further studies are not required. Overview based on literature review is appropriate.

III.2 Pharmacokinetics

The MAH provided a literature review. In addition, two distribution studies were provided (Report APS/81 and Report 118/TN) to support the original market application in 1985. These studies demonstrated that at 18 hours post administration the highest radioactive content (79%) was seen in the small intestine. Eight days post administration, there was no retention of radioactivity or any residual accumulation in organs. Excretion occurred via the faeces and was greater than 95%.

III.3 Toxicology

The nonclinical toxicology data to support the original market application in 1985 included three extended single dose toxicity studies in rats. All studies were non-GLP as they were conducted before the current regulations were established. The results of the three studies show no deaths. Furthermore, no overt signs of toxicity were observed when the compound was administered either orally or intravenous (i.v.) at doses of approximately 20.000 times the maximum human dose of 30 µg (0.5 µg/kg for a 60 kg human). When adjusted for body surface area using a conversion factor of 6.2 (Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA)) this equates to a safety margin of 3226. Considering the endpoints evaluated, the no observed adverse effect level (NOAEL) for these studies is considered to be 10 mg/kg.

III.4 Ecotoxicity/environmental risk assessment (ERA)

The MAH provided an environmental risk assessment (ERA) in which the $PEC_{surfacewater}$ for SeHCAT was calculated to be 8.2×10^{-6} µg/L. This value is lower than the specified action limit of 0.01 µg/L. For the octanol/water partition coefficient (Log K_{ow}) a calculated value is generally not accepted, as outlined in question 6i of the Q&A on the ERA guideline (EMA/CHMP/SWP/44609/2010 Rev. 1). Given the small annual consumption and the technical challenges involved in obtaining an experimental value as described below, this is not considered a general case and therefore, the requirements stated in the guideline may be omitted in this case. Using two different QSAR software programs, theoretical calculations of the Log K_{ow} were performed for SeHCAT, in addition to calculated values for taurocholic acid used as reference. The test and reference have analogue chemical structures which makes highly unlikely that these bile acid analogues will have vastly different Log K_{ow} values. The experimentally obtained partition coefficient for the ionised taurocholic acid is -0.50 (Roda et al., 1990), which compares favourably with the theoretical calculated value. The results, which show Log K_{ow} values between -1 and 0.4, are well below the threshold of 4.5 and provide

further confirmation that SeHCAT is not likely to bioaccumulate in aquatic organisms nor be readily partitioned into organic detritus in the aquatic environment.

Conclusions on studies

Based on the low Log K_{ow} value and the low $PEC_{surfacewater}$, SeHCAT is expected to have no significant bioaccumulation potential. As there are no other environmental concerns, the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients and a Phase II environmental assessment of SeHCAT is not required.

III.5 Discussion on the non-clinical aspects

The MAH submitted a literature review and has not provided additional studies; no further studies are required. The submitted non-clinical overview to support the pharmacology, pharmacokinetics and toxicology of SeHCAT is adequate and is of sufficient high quality in view of the present European regulatory requirements.

IV. CLINICAL ASPECTS

IV.1 Clinical pharmacology

Upon ingestion of the SeHCAT hard capsule, it travels to the stomach where it becomes rapidly hydrolysed, releasing its contents into the gastrointestinal tract. SeHCAT travels along the gastrointestinal tract until it reaches the terminal ileum where it is actively absorbed. The stably associated taurine in SeHCAT ensures that the degree of passive transport is minimised. Active transport facilitates the trafficking of SeHCAT into the enterohepatic system in which it cycles like a normal bile acid. Due to the lack of passive reabsorption of SeHCAT, the degree of bile acid malabsorption becomes a function only of the degree of active uptake of bile acids. There are no secondary pharmacodynamic properties associated with SeHCAT or with its excipients.

No data have been published detailing the alteration of SeHCAT pharmacodynamics with any other pharmaceutical.

The radio-labelled characteristics of SeHCAT allow an easy assessment of the enterohepatic circulation of this tracer. Counting may commence immediately post-administration of the 370 kBq capsule with a glass of water. A latent period of 30 to 40 minutes is normally seen before the activity starts to pass out of the stomach. Though, this rate is variable and subjected to patient position, stomach contents and other such factors. In healthy patients, the gall bladder will be visualised in 1 to 3 hours, depending on the individual. After overnight fasting, the gall bladder should be clearly visualised. Excretion of SeHCAT follows a bi-exponential curve, as described by Nyhlin (Nyhlin et al., 1983). SeHCAT behaves much like natural bile, except that it does not readily become deconjugated. Therefore, SeHCAT does have the ideal pharmacokinetics to produce an accurate and differential diagnosis of bile acid malabsorption.

IV.2 Clinical efficacy

SeHCAT is a radiopharmaceutical that has been proposed for measuring bile acid pool loss and investigating bile acid malabsorption. It can also be used to assess ileal function, investigate inflammatory bowel disease (IBD) and chronic diarrhoea and study the enterohepatic circulation. This means, that all patients presenting the above-mentioned conditions might be good candidates for such a test, which has been used in clinical conditions across Europe for more than 20 years. SeHCAT is not used for the diagnosis of chronic diarrhoea but aims at identifying the underlying cause of this chronic diarrhoea, which is frequently underestimated or lately suspected. Many studies conducted from the time of release demonstrate the role of SeHCAT. Below is an overview of some of these studies.

As reported here below, SeHCAT use cannot be considered independently from the medical history of the patient and other examinations. The recent British Society of Gastroenterology (BSG) guidelines (Arasaradnam et al., 2018) together with the paper from Bares (Bares et al., 2017) provide an appropriate use of this SeHCAT retention rate in the diagnostic workflow of patients with chronic diarrhoea associated with IBD-D. SeHCAT is not used for diagnosing ileal disease. However, since the reabsorption of bile acids occurs at that level, any dysfunction of the ileum will significantly impact the retention rate measured by SeHCAT. Therefore, it is not surprising to observe that Crohn's disease with the involvement of the terminal ileal portion is frequently associated with bile acid malabsorption (BAM), this being almost constant when this portion is surgically removed. This has been well observed in various studies (e.g., Nyhlin et al., 1983; Fagan et al., 1983).

Since there is no direct comparator for establishing the diagnosis of bile acid malabsorption/diarrhoea (BAM/BAD), except for the historical faecal bile acid test, some surrogate reference standards have been used to confirm the place and value of SeHCAT in the diagnostic chart of patients presenting clinical symptoms of chronic diarrhoea compatible with this diagnosis. If a cholestyramine test (reported as trial by treatment) has been historically proposed for identifying patients with BAM/BAD, the limited tolerability of cholestyramine and its limited efficacy in patients presenting low SeHCAT retention rate, have significantly hampered its diagnostic use leading to a complete abandonment.

In a recent survey, it was reported that 16% of gastroenterologists and 22% of general practitioners in five European countries were unable to make a diagnosis of IBS-D, with an incorrect diagnosis in 12% and 14 % of cases respectively (Andresen et al., 2015). Diagnosis of BAM is a difficult and unpleasant procedure, as it is a 24-hour measurement of faecal bile acids. Besides, this definitive method is only available in a few research laboratories. The ^{14}C glycocholate breath test is of historical interest due to its limited clinical utility. The measurement of the serum bile acid precursor 7α-OH-4-cholesten-3-one (7aC4) and serum levels of FGF19 might be of interest in the future when fully validated and widely available. A significant advantage of SeHCAT over the other biomarkers has been reported. Indeed, since the retention of SeHCAT is measured after 7 days, this is taking into account multiple bile acid recirculation's (around 35) while the measurement for the other biomarkers is instantaneous. This is of value, as it is well known that this recirculation is irregular by essence leading to erroneous measurements provided by blood biomarkers. The systematic review and meta-analysis performed by Valentin (Valentin et al., 2017) included 36 studies enrolling 5028

patients. It was demonstrated that among patients with functional bowel disorders (FBD) with diarrhoea (IBS-D or functional diarrhoea), there is a consistent prevalence of positive tests that are suggestive of BAD (malabsorption or increased bile acid synthesis) in ~25% averaged over all studies and all methods. The average prevalence of a positive test was 30.8% for ^{75}SeHCAT using <10% retention, 25.5% for total 48-hour faecal BA, 24.8% for serum FGF19 and 17.1% for serum C4. These data confirm the importance of including an evaluation for abnormal bile acid homeostasis (synthesis or excretion) in patients with IBS-D or functional diarrhoea. The results also confirm Camilleri's recommendation (Camilleri, 2015) that given the relative prevalence of BAD (~25% of 5% IBS-D/functional diarrhoea in Western countries, i.e., 1.25%) compared with diarrhoea of coeliac disease (~0.8%), testing for BAD is indicated in these patients, as is screening for coeliac disease.
The 7-day ^{75}Selenium homocholic acid taurine (SeHCAT) test is therefore considered as the most appropriate for clinical practice (Aziz et al., 2015; Bajor et al., 2008; Bajor et al., 2015; Barkun et al., 2013; Mottacki et al., 2016; Shin et al., 2013; Sinha et al., 1998; Slattery et al., 2015; Smith et al., 2000; Smith and Perkins, 2013; Arasaradnam et al., 2018).

Available data from clinical studies in more than 3000 patients with prospective and retrospective assessments, support the clinical importance of using ^{75}Se-HCAT scanning for investigating the enterohepatic circulation of bile acid pool with associated loss or abnormal turnover and bile acid malabsorption, as a consequence of abnormal ileal function and inflammatory bowel disease in patients presenting chronic diarrhoea.

The first observational and prospective studies were performed in the 1980's assessing healthy controls and patients with either Crohn's disease with or without associated ileal resection or chronic diarrhoea. This allows identifying a normal retention rate above 20%. Besides, three retention levels of 5, 10 and 15% have been validated for classifying this disease as: severe, moderate and mild BAM respectively, with significant differences from healthy controls. As such, using a lower limit of 15% retention gave a specificity of 0.99 and an upper limit of 8% was associated with a sensitivity of 0.97 to assess bile acid malabsorption with an accuracy of 0.88, in the population studied of 106 patients with suspected BAM (Merrick et al., 1985). There is a consensus for a diagnostic threshold at 10% since 1991 and a study conducted by Williams (Williams et al., 1991). This is supported by several papers and guidelines. It is true that a population of patients presenting a retention rate between 10 and 15% could respond to some treatments, but this is significantly lower than below 10%. This is also supported by the SeHCAT dose-response relationship according to malabsorption (M) severity (7). The Wedlake review (Wedlake et al., 2009), confirmed by Riemsma (Riemsma et al., 2013), indicated the score of malabsorption and its correlation with the treatment response as: severe malabsorption <5%: 96% response; severe/moderate M <10%: 80% response; severe/moderate/mild M<15%: 70% response. This kind of threshold are included in the most recent SPC (Italian SPC 2018) because it has been confirmed by two different studies with patients with irritable bowel syndrome (IBS) (Bajor et al., 2015) and oncologic patients (Gupta et al., 2015). The 10% threshold is aligned with the practice reported by Summers in their survey in 38 UK centres (Summers et al. 2016). Indeed, for patients with <5% SeHCAT retention, 96% (n=185/193) had a centre-defined 'abnormal' result, as did 91% (n=110/121) of those with a SeHCAT retention of 5% to <10%. For patients with a SeHCAT retention of 15% or more, 92% (n=381/412) had a centre-defined 'normal' result. Those

patients whose SeHCAT retention score lay in the range 10% to <15% were divided between the 'abnormal' (59%, n=56/95) and 'borderline' (35%, n=33/95) centre-defined categories.

These results have been confirmed in large studies conducted in European countries where the product is available. Prospective studies have been conducted with different patient groups (Aziz et al., 2015; Bajor et al., 2008; Bajor et al., 2015; Fellous et al., 1994; Orekoya et al., 2015; Pattni et al. 2013). They enrolled in total 496 patients with chronic diarrhoea with or without Crohn's disease and with or without ileal resection. The results are consistent with a significant prevalence of low retention rate (typically below 5%) in patients with Crohn's disease with or without ileal resection, the latter clinical presentation being associated almost systematically with a severe BAD assessed by retention rate below 5%. A consistent prevalence of BAM of around 30% in patients classified as IBS-D (with positive Rome III criteria) has been reported. The retrospective studies involving a total of 1892 patients identified the same characteristics in similar patient groups (Borghede et al., 2011; Gracie et al., 2012; Kurien et al., 2011; Orekoya et al., 2015; Phillips et al., 2015; Wildt et al., 2003).

One study done by Fellous (Fellous et al., 1994) reported that the sensitivity and specificity were 0.79 and 0.90 respectively, with a positive and negative predictive value (PPV, NPV) of 0.93 and 0.72 respectively, when considering a threshold of 8% in 76 patients and controls. Two adequate meta-analyses comprising a total of 2131 patients reported for the first analysis a prevalence of idiopathic BAM/BAD between 10% (CI: 7–13) using a threshold of 5% at day 7 for SeHCAT (severe malabsorption), 32% (CI: 29–35) using a threshold of 10% (severe and moderate malabsorption) and 26% (CI: 23–30) using a threshold of 15% (severe, moderate and mild malabsorption). Rates for the second study vary from 16.9% to 35.3% (Slattery et al., 2015; Wedlake et al., 2009). Therefore, its use in type-1 BAM may be less useful since almost all tested subjects with ileal disease and/or resection are predictably positive to this test (more than 80%) and therefore candidates for an immediate targeted treatment. Conversely, the reported prevalence of BAM in patients classified as IBS-D (with positive Rome III criteria) of around 30% and BAM type III (with a large spectrum of disease), calls for this test before proposing an appropriate treatment that will provide a prompt relapse of symptoms ultimately. Moreover, the test is highly reproducible, avoiding for any repeat along patients' follow- ups (Bajor et al., 2008; Fellous et al., 1994).

SeHCAT testing is clinically useful in tailoring treatment for patients with unresected ileal disease. Three bile acid sequestrants (BAS) are commercially available but not in all countries. These are cholestyramine and colestipol, which are most commonly used and the most recently available colesevelam. Other non-BAS therapy includes aluminium hydroxide and the new farnesoid X receptor (FXR) agonist obeticholic acid, which has undergone its first proof-of-concept clinical trial in the context of BAM, considerably enlarging the treatment palette for these patients. The reliable positive ^{75}Se- HCAT testing bring the added knowledge of a definitive diagnosis of BAM, this would therefore encourage BAS initiation and continuation with tailoring of BAS by dosage adjustment or drug switching. The grade of severity as established by the three retention thresholds 5, 10 and 15% appears as a prognostic factor for a positive response to targeted treatment, with a strong difference in response rates between a positive SeHCAT (on average 85% (74% to 100%), 73% and 72% (62% to 86%) for cut-offs at 5%, 10% and 15%, respectively) and a negative test (14% at a cut-off of 5% and 0% at a cut-off of 15%) (Riemsma et al., 2013). However, the three studies only provided data on the

effectiveness of BAS given a negative SeHCAT test, while 19 studies were considered in this meta-analysis (Riemsma et al., 2013). Since that meta-analysis new well-controlled studies (with one multicentre study) involving 855 patients have been conducted, reporting a successful response (based on symptoms improvement) in the range of 63 to 70% when the retention rate is below 10%. The response rate decreased with decreased severity of BAM/BAD (Gupta et al., 2015; Orekoya et al., 2015). Utilising SeHCAT scanning would therefore guide clinical expectations of limited response in patients with mild-to-moderate BAM. Likewise, by utilising the SeHCAT test, clinicians can therefore avoid unnecessary trials of unpalatable cholestyramine in patients without BAM or falling into a trap of relying on false negative 'cholestyramine trials' in patients with BAM who have no motivating diagnosis and promptly stop. Empirically offering this agent without a diagnostic justification or driver is highly unlikely to prove effective.

The recent BSG guidelines issued by Arasaradnam (Arasaradnam et al., 2018) emphasised the role of SeHCAT in patients with IBS. Patients with very low ^{75}SeHCAT values are most likely to have a response to treatment with bile acid sequestrants. They recommend trying this if the ^{75}SeHCAT value is <15% or the fasting serum C4 is raised above defined laboratory values (Grade of evidence level 2, Strength of recommendation strong). As such, the use of SeHCAT would significantly reduce the time-to-diagnosis when introduced early in the diagnostic chart of patients with chronic diarrhoea. By offering them a short delay until diagnosis, minimised unnecessary cost expenditure on clinics and negative investigations, limited number of hospitalisations, and limited associated social costs. On top of that, the availability of this test would ease patient management by primary care physicians and limits the involvement of secondary care physicians with additional costs. Nowadays, SeHCAT is considered as the standard of reference for diagnosis BAM in guidelines and recommendations despite its unavailability in many countries with the risk of under diagnosing BAM in these populations. The British Society of Gastroenterology proposed the use of SeHCAT test in patients with IBS or chronic diarrhoea when in both cases a BAM is suspected (Soundy et al., 1982; Spiller et al., 2007; Thomas et al., 2003; Arasaradnam et al., 2018). Likewise, a working party supported by the American College of Gastroenterology acknowledged that in Europe measurement of whole-body retention of a radioactive bile acid, SeHCAT, is the most widely available test for BAM despite some controversy over its diagnostic utility (Schiller et al., 2014).

IV.3 Clinical safety

The absorbed radiation dose from SeHCAT is low, as demonstrated by the Nyhlin's estimated dose of 0.2 µGy/kBq for whole body dose (Nyhlin et al., 1983). Critical organ doses (to the ileum and gall bladder) were estimated to be 3.2 µGy/kBq (Soundy et al., 1982). According to the International Commission on Radiological Protection (ICRP) 80, oral administration of SeHCAT to a patient of 70 kg body weight results in an Effective Dose of 0.7 mSv/MBq. As expected, the small intestine and colon receive the largest dose, though 0.74 mGy per 370 kBq administration is regarded as very low. With such low doses, any arising pathologies as a result of the activity used are not expected. For this product, the effective dose to a healthy adult resulting from the administration of a 370 kBq capsule is typically 0.26 mSv. This is far below the effective dose reported for abdominal X-ray (0.5 to 0.7 mSv) an abdominal CT-scan (10 mSv), or a hepato-biliary scintigraphy with 111 MBq of 99mTc-Mebrofenin SCO (2.7 mSv) (Health Physics Society, 2010).

Regarding a reported toxicity of selenium, this is observed for very high doses of ingested selenium only. The human lethal dose is estimated between 0.5 and 1 g per day as selenite or sodium selenite based on animal data demonstrating a significant safety margin. In the present case, since each capsule contains 0.07 mg of tauroselcholate, the amount of selenium is in the range of the recommended daily dose in humans. Therefore, no toxicity related to this element is foreseen, this being reinforced by its single dose administration.
No preclinical and clinical data have been found to support the use of SeHCAT in human pregnancy. In addition, no preclinical and clinical data exist regarding the transfer of SeHCAT via human milk. Therefore, SeHCAT should not be administered to pregnant or lactating mothers unless it is considered that the benefits outweigh the potential hazards. No studies were performed on juvenile animals during the preclinical development phase. No studies have been performed in developing children and the use of ionising radiation is a potential hazard even at very low doses, consequently SeHCAT is contraindicated for use in children. No information is available on exposure of populations with specific racial and/or ethnic origins.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to SeHCAT 370 kBq.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	Use during pregnancy and lactation

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.5 Discussion on the clinical aspects

For this application, no new clinical studies were conducted. The MAH submitted data available from the literature on the pharmacology of SeHCAT. Risk management is adequately addressed. Based on the data, the necessary warnings and recommendations have been included in the SmPC of the medicinal product. Overall, this medicinal product can be used for the specified indications. The clinical aspects of this product are approvable.

V. USER CONSULTATION

The package leaflet (PL) 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. The language used for the purpose of user testing the PL was Dutch.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the parent leaf Myoview 230 micrograms kit for radiopharmaceutical preparation, powder for solution for injection (RVG 16323) and AdreView 74 MBq/ml solution for injection (RVG 57689). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

SeHCAT 370 kBq hard capsules has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements. The overall benefit-risk is considered approvable.

The Board followed the advice of the assessors.

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 the risk-benefit balance for SeHCAT is positive and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 26 April 2023.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5413/ 001/IB/001	Change in control of the Finished Product: - Other variation.	No	6-12-2023	Approved	N.A.
NL/H/5413/ IB/002/G	Replacement or addition of a site where batch control/testing of the finished product takes place.	No	2-5-2024	Approved	N.A.
NL/H/5413/ IB/003/G	Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier). Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient: New certificate for a starting material/reagent/ intermediate/or excipient from a new or an already approved manufacturer.	No	21-06-2024	Approved	N.A.