National Institute for Health and Clinical Excellence

Diagnostics Assessment Programme

SeHCAT (TAUROSELCHOLIC [^{75} SELENIUM] ACID) FOR THE INVESTIGATION OF DIARRHOEA DUE TO BILE ACID MALABSORPTION

Final scope

December, 2011

1. Introduction

The Medical Technologies Advisory Committee (MTAC) identified SeHCAT ([^{75}Se] tauroselcholic acid) (GE Healthcare) as potentially suitable for evaluation by the Diagnostics Assessment Programme (DAP) on the basis of a briefing note that included a description of the purpose of the technology as detailed below.

The scope outlines the approach for assessing the clinical and cost-effectiveness of SeHCAT.

2. Description of the technology

This section describes the properties of the technology based on information provided to NICE by the manufacturer and on information available in the public domain. NICE has not carried out an independent evaluation of these descriptions.

2.1. Purpose of the medical technology

SeHCAT is a radiopharmaceutical that is licensed for use in measuring bile acid pool loss and investigating bile acid malabsorption (BAM). It may also be used to assess ileal function, to investigate Inflammatory Bowel Disease (IBD) and chronic diarrhoea and to study enterohepatic circulation.

2.2. Product properties

SeHCAT is a diagnostic radiopharmaceutical which consists of a capsule containing a synthetic analogue of the natural conjugated bile acid tauroselcholic acid and ^{75}Se

(a gamma-emitter). The radionuclide tracer atom allows SeHCAT to be easily detected in a whole body scan using a standard gamma camera. The technology is used to test the function of the bowel by measuring how well the compound is retained or lost from the body into the faeces. It is claimed that SeHCAT is the only test available to diagnose BAM.

The test involves two scans one week apart, and these are carried out as outpatient appointments. During the first appointment, SeHCAT is administered orally and, once localised in the body (after approximately one to three hours), the radionuclide tracer atom is detected in a whole body baseline scan using a standard gamma camera. This gives an initial count which is used to provide a zero-time or 100% value. During the second appointment, the patient is scanned to produce a second count and the retained activity is expressed as a percentage of the original value. A retention value of less than 10% is considered abnormal and indicative of BAM.

Appendix C contains the summary of product characteristics.

3. Target condition/indication

The target condition/indication for this assessment is chronic diarrhoea due to bile acid malabsorption (BAM). Diarrhoea can be defined as the abnormal passage of loose or liquid stools more than three times daily and/or a volume of stool greater than 200g/day and is considered to be chronic if it persists for more than 4 weeks (Thomas *et al,* 2003). The cause of chronic diarrhoea in adults is difficult to ascertain and patients may undergo several investigations without a definitive cause being identified (Sinha *et al,* 1998). Chronic diarrhoea is one of the most common reasons for referral to a gastrointestinal clinic (Smith et al, 2000), and could account for as many as 1 in 20 referrals. Estimates of the prevalence of chronic diarrhoea in a Western population are 4-5% (Patient UK, 2009). Some of the causes of chronic diarrhoea are given in table 1 below.

BAM is one of several causes of chronic diarrhoea (see table 1) and results from failure to absorb bile acids (which are required for the absorption of dietary fats and sterols in the intestine) in the distal ileum. Normally, more than 90% of the acids are

reabsorbed in the distal ileum. BAM results in excess bile acids in the colon where they cause diarrhoea by various mechanisms. These mechanisms include:

i. Inducing secretion of sodium and water particularly at a concentration above 3mmol/l

ii. Increase colonic motility

iii. Stimulating defecation

iv. Inducing mucus secretion

v. Damage to mucosa thereby increasing mucosal permeability.

BAM has been divided into 3 types depending on aetiology:

i. Type 1: Following ileal resection, disease or bypass of the terminal ileum

ii. Type 2: Primary idiopathic malabsorption

iii. Type 3: associated with cholecystectomy, peptic ulcer surgery, chronic pancreatitis, celiac disease and diabetes mellitus.

Table 1: Causes of diarrhoea (Thomas *et al,* 2003)

Colonic
Colonic neoplasia
Ulcerative and Crohn's colitis
Microscopic colitis
Small bowel
Coaliac disease
Crohn's disease
Other small bowel enteropathies (for example, Whipple's disease, tropical sprue, amyloid, intestinal lymphangiectasia)
Bile acid malabsorption
Disaccharidase deficiency
Small bowel bacterial overgrowth
Mesenteric ischaemia
Radiation enteritis
Lymphoma
Giardiasis (and other chronic infections)
Pancreatic
Chronic pancreatitis
Pancreatic carcinoma
Cystic fibrosis
Endocrine
Hyperthyroidism
Diabetes
Hypoparathyroidism
Addison's disease
Hormone secreting tumours (VIPoma, gastrinoma, carcinois)
Other
Factitious diarrhoea
"Surgical" causes (e.g. small bowel resection, internal fistulae)
Drugs
Alcohol
Autonomic neuropathy

3.1. Irritable Bowel Syndrome (IBS)

People with chronic diarrhoea are often diagnosed as having diarrhoea predominant irritable bowel syndrome (D-IBS or IBS-D) if a definitive cause has not been identified. There is evidence that suggests a high prevalence of bile acid malabsorption (up to one third) in patients previously diagnosed with D-IBS (Galatola

et al, 1992 and Smith *et al*, 2000). On this basis, approximately half a million patients in the NHS who are currently treated for D-IBS actually have BAM for which potential diagnosis and effective treatment are available (Wedlake et al, 2009).

IBS is one of the most common functional gastrointestinal disorders. It is a chronic, relapsing and often life-long disorder, characterised by the presence of abdominal pain/discomfort associated with defecation, a change in bowel habit together with disordered defecation (constipation or diarrhoea or both), the sensation of abdominal distension, and can include associated non-colonic symptoms. These morbidities can cause dehydration, lack of sleep, anxiety and lethargy, with consequences such as time taken off work, avoidance of stressful or social situations and significant reduction in quality of life (NICE Clinical Guideline 61: Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care).

IBS most commonly affects people between the ages of 20 and 30 years and is twice as common in women as in men. People with IBS are the largest group of patients seen in a general gastroenterology clinic (1 in 20 referrals). The prevalence of the condition in the general population is estimated at between 10 and 20%. Recent trends indicate that there is also a significant prevalence of IBS in older people, therefore IBS diagnosis should be a consideration when an older person presents with unexplained abdominal symptoms. The true prevalence of IBS in the whole population may be higher than estimated, because it is thought that many people with IBS symptoms do not seek medical advice; NHS Direct online data suggest that 75% of people using this service who have IBS symptoms rely on self-care. In England and Wales, the number of people consulting for IBS is extrapolated to between 1.6 and 3.9 million (NICE Clinical Guideline 61).

3.2. ***Inflammatory Bowel Disease***

Ulcerative Colitis and Crohn's Disease are the two most common forms of Inflammatory Bowel Disease (IBD). Together these long-term conditions are estimated to affect about 240,000 people in the UK, approximately 400 per 100,000

population (Rubin et al, 2000). Both ulcerative colitis and Crohn's disease directly cause chronic diarrhoea.

Crohn's disease is a chronic severe condition characterised by inflammation, ulcers and bleeding which may affect any part of the gastrointestinal tract, mostly the terminal ileum. There are approximately 60,000 people in the UK with this condition (Patient UK, 2011). Crohn's disease is sometimes treated by ileal resection. In a study carried out by Smith *et al* (2000) BAM was found in 97% of people with Crohn's disease with ileal resection who were in clinical remission and in 54% of people in clinical remission with unoperated Crohn's disease.

4. Scope of the evaluation

4.1. Population

The two population groups included in this evaluation are:

a) People with Crohn's disease and chronic diarrhoea who have not undergone ileal resection.
b) People presenting with chronic diarrhoea with unknown cause.

4.2. Intervention

The notified technology for this intervention is SeHCAT.

4.3. Potential alternative technologies

This section describes alternative technologies that were identified during early scoping. The suitability of including these technologies in the assessment was discussed at the scoping workshop and at the assessment subgroup meeting.

4.3.1. Plasma lathosterol

This test can be used to diagnose BAM in people with Crohn's disease with ileal resections of varying length (Färkkilä *et al,* 1996). The concentration of plasma lathosterol is known to reflect cholesterol and bile acid synthesis. At the scoping workshop, there was agreement that this test is not suitable for inclusion in the evaluation because it is not thought to be currently under consideration for use in the NHS.

4.3.2. Cholestenone

The serum 7-alpha-hydroxy-4-cholesten-3-one test may be an alternative technology within this assessment. However it is currently only available in specialist centres or as a research procedure and will therefore, not be included in the evaluation.

4.3.3. Trial of treatment

In the absence of diagnostic tests, a therapeutic trial of aluminium hydroxide or bile acid sequestrants (BAS), such as cholestyramine, is sometimes employed to diagnose BAM. The value of this approach has not been the subject of study (Thomas et al, 2003). Therapeutic trials of cholestyramine lack diagnostic accuracy since the optimal dose is not predictable and false negative rates of 25% have been reported. Discussions at the scoping workshop and the assessment subgroup meeting affirmed that trial of treatment is not a routine diagnostic technique and that BAS are not always tolerated by patients. Trial of treatment will not be considered as an alternative technology in this evaluation.

4.3.4. Faecal bile acids

This method is based on measuring the amount of faecal bile acids in a 24 hour stool collection. Bile acid levels greater than 1.2 mmol/l are considered to be abnormal. The scoping workshop was informed that the difficulties of organising 24 hour faecal collection have restricted the use of this test to specialised research laboratories. As a result, faecal bile acids measurement will not be included in this evaluation.

4.4. Comparator

There is no direct comparator for this diagnostic test. Current diagnostic options include analysis of a patient's history, investigations to exclude 'red flag' symptoms and a variety of other diagnostic tests such as blood tests and lactose tolerance tests. Trial of treatment is used, with mixed results, to diagnose BAM. It is however, not widely used in current practice.

The main comparator for the assessment will be tests and clinical observations contained in the British Society of Gastroenterology (BSG) guidelines for the investigation of chronic diarrhoea (Thomas *et al*, 2001) (see section 4.6).

4.5. Healthcare setting

The assessment will focus on the use of SeHCAT in secondary care.

4.6. Care pathway

4.6.1. **Diagnosis**

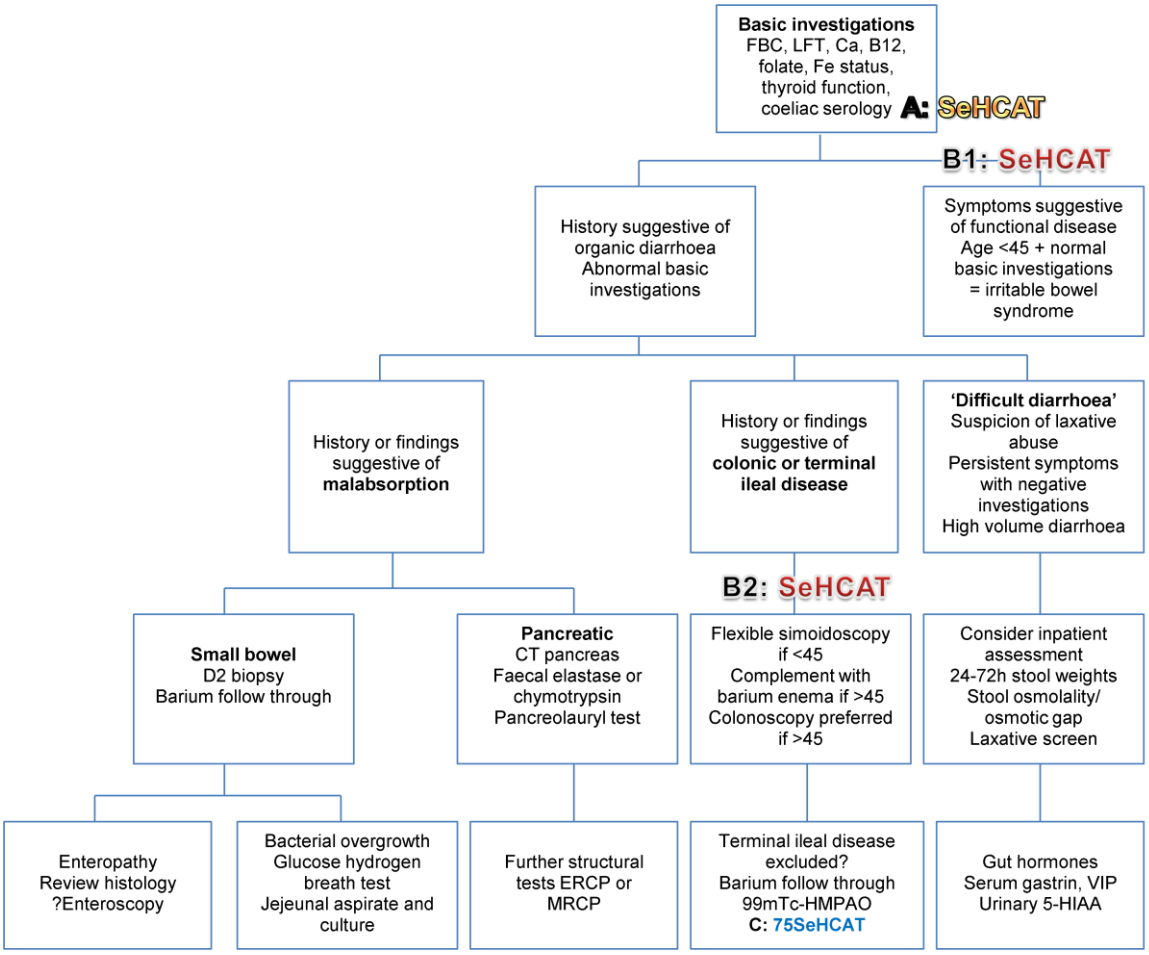
Patients with undiagnosed BAM are likely to present with chronic diarrhoea. The BSG guideline states that bile salt malabsorption occurs when normal active uptake from the ileum is disrupted by ileal inflammation or resection. It also states that the degree of malabsorption depends on the length of ileal involvement or resection. According to the BSG guidelines, diagnosis of BAM can be made via SeHCAT scanning.

During early scoping, two issues arose regarding the BSG pathway. First, all experts agreed that SeHCAT needs to be placed earlier in the pathway to help patients gain a firm diagnosis at an earlier stage. However, expert opinion varied as to where SeHCAT should be placed on the pathway. Some felt that it should be available to GPs for use in all patients with chronic, erratic bowels with a tendency to diarrhoea, while others felt that it is more appropriate for use in secondary care. Second, the BSG guideline does not take into account the prevalence of BAM in people diagnosed with IBS. The BSG guideline places SeHCAT at the end of the diagnostic algorithm (position C in Figure 1). Possible alternatives are:

1. SeHCAT as part of the basic investigations for all patients presenting with chronic diarrhoea (position A in Figure 1);
2. SeHCAT for all patients presenting with chronic diarrhoea and symptoms suggestive of functional disease (i.e. age < 45 and normal basic investigations) (position B1 in Figure 1); and also for patients with a history of findings suggestive of colonic or terminal ileal disease (position B2 in Figure 1).

Figure 1:

BSG Guideline for the investigation of chronic diarrhoea (Thomas et al. 2003)



SeHCAT as part of the basic investigations (position A in Figure 1), means that all patients presenting with chronic diarrhoea will be tested with SeHCAT. However, during the scoping workshop clinical experts advised that a positive SeHCAT test at this stage does not rule out the possibility of organic disease. As no subsequent tests for organic disease are made redundant, it is unlikely that SeHCAT in position A will be more cost-effective than in position B1. Therefore, this assessment will focus on position B1.

The same applies to SeHCAT in position B2. A positive SeHCAT test in position B2 is not thought likely to stop clinicians from doing subsequent tests such as sigmoisdoscopy, barium enema or colonoscopy. Therefore, in the assessment, using

SeHCAT in position B2 and in position C will be considered as having the same effect on the care pathway.

This leaves two possible populations for investigation:

1. People presenting with chronic diarrhoea with unknown cause and symptoms suggestive of functional disease;
2. People with Crohn's disease and chronic diarrhoea with unknown cause (i.e. before resection of the terminal ileum)

4.6.2. **Treatment**

Following a definitive diagnosis, patients may be treated with bile acid sequestrants which can cause significant reduction in bowel frequency and therefore a better quality of life (Pattni & Walters, 2009). There are currently two types of bile acid sequestrants available:

a) Bile binding resins (colestyramine and colestipol): although they are tolerated by some, most people dislike these treatments because of side effects and the difficulty of administration, but take them in the long term because they can help in managing the condition. One in four patients cannot take more than a single dose.
b) Colesevelam (gel matrix): Two thirds of patients take this treatment for at least 4 years and most of those who stop do so because they found no benefit initially.

The response to bile acid sequestrants therapy varies among people with bile acid diarrhoea. For those with Crohn's disease with ileal resection, the response to BAS was 60%, 40% in those with Crohn's disease without ileal resection and 70% in those with a diagnosis of D-IBS (Smith *et al,* 2000).

5. Modelling approach

5.1. Modelling possibilities

The aim and structure of the model will depend upon the final scope and the nature of the data available. The diagnostic pathway to be modelled in the assessment will depend on the prevalence of BAM in the population as well as the costs and side

effects of the tests, the test accuracy and the probability of diagnosing a condition and not needing to carry out more tests.

5.2. Model structure

Since no end-to-end studies that measure the clinical utility of SeHCAT from initial diagnosis through to final health outcomes were identified during the scoping phase, a linked evidence approach to modelling is the most likely scenario. The intermediate measures and direct outcomes of the diagnostic strategies employed will need to be related to changes in treatment decisions, any delays in diagnosis and final health outcomes.

An outline of the models proposed by the External Assessment Group (EAG) is given below.

Figure 2: Outline of model for patients presenting with chronic diarrhoea with unknown cause and symptoms suggestive of functional disease

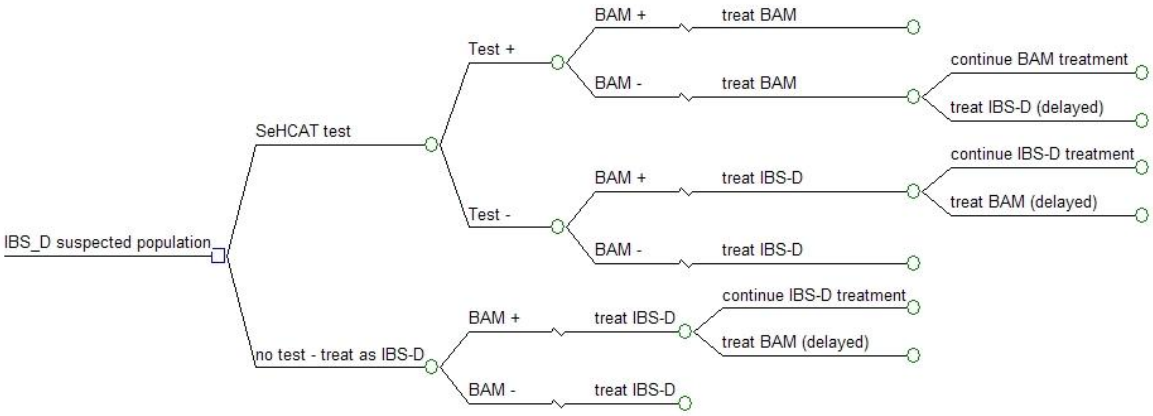
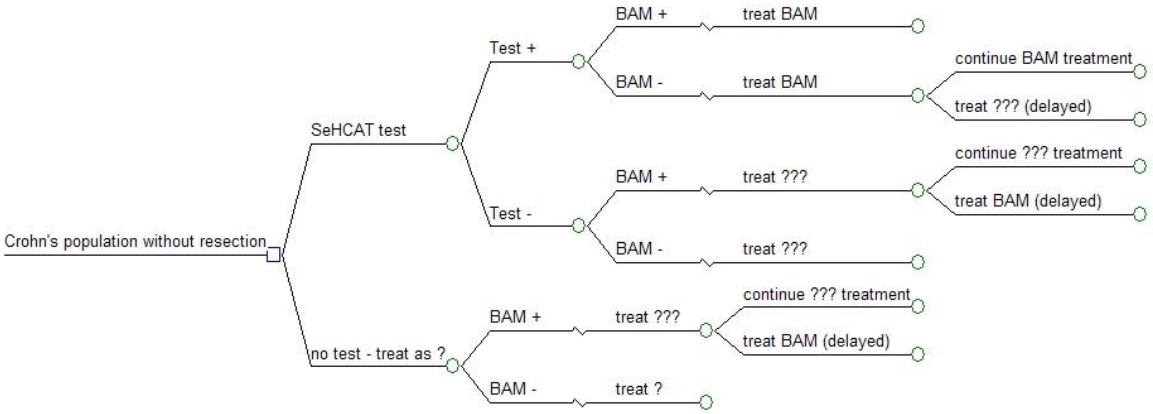


Figure 3 Outline of model for patients with Crohn's disease and chronic diarrhoea with unknown cause (i.e. before resection of the terminal ileum)



Final choices and definitions regarding the structure of the model will depend on the findings from the literature review and consultation with clinical experts. In addition, the existence/availability of any other electronic models that reflect the cost-effectiveness of treatment pathways for these patients, and are representative of current care in the NHS, will be determined by the EAG.

5.2.1. Health outcomes

The following outcomes will be considered:

- Effect of testing on treatment plan (e.g. surgical or medical management), where information on the appropriateness of the final treatment plan is also reported
- Effect of testing on clinical outcome (e.g. morbidity and adverse events)
- Prognosis - ability of test result to predict clinical outcome (e.g. response to treatment).

For included studies reporting any of the above outcome measures, the following outcomes will also be considered if reported:

- Acceptability of tests to patients or surrogate measures of acceptability (e.g. waiting time and associated anxiety)
- Adverse events associated with testing (e.g. pain/discomfort experienced during the procedure and waiting times before results).

Utility values, based on literature or other sources, will be incorporated in the economic model. QALYs will be calculated from the economic modelling.

5.3. Cost considerations

	Notified technology
Indicative price of technology	£195
Consumables (if applicable) *Per consumable: name, list price, average/range selling price, frequency*	N/A
Service/maintenance cost and frequency (if applicable)	£55 -£105
Anticipated life span of technology	Each capsule has a shelf life of 12 weeks once only
Average length of use per treatment	N/A
Average frequency of use	Once only
Cost of administration	£186
Average cost per test	£436 - £486

The costs in the above table were provided by the manufacturer in their notification to MTAC. At the scoping workshop and assessment subgroup meeting, there was uncertainty regarding the cost of service and maintenance.

SeHCAT capsules costs £195 per patient (and therefore per treatment). The total cost of the intervention estimated by the manufacturer also includes the use of the gamma cameras in the nuclear medicine department. The tariff for administering this diagnostic test in the NHS is around £186 (HRG RA36Z nuclear medicine cat 2, OPCS code - U172, Non-mandatory national tariff 2011/12).

There is no direct comparator for this diagnostic test; other options include analysis of a patient's history, investigations to exclude 'red flag' symptoms and a variety of other diagnostic tests such as blood tests and lactose tolerance tests.

When the SeHCAT test provides a positive diagnosis of BAM, further investigations may not be necessary, which could result in savings through reduced GP appointments, fewer gastrointestinal clinic appointments and a reduction in the number of diagnostic tests carried out. For indication, a GP appointment costs around £32 (Unit costs of health and social care, 2010). A gastroenterology outpatient first appointment costs £287 while a follow-up outpatient appointment

costs £90 (Non-mandatory national tariff, treatment function code 301). The costs of further diagnostic tests vary but savings may be achieved by avoiding unnecessary tests.

If nuclear medicine departments are already running at, or close to capacity, additional capital funding may be required to increase capacity. There will be a limited amount of training required by clinicians using SeHCAT. It is not anticipated that this technology will have any further impact on facilities.

Resource utilisation will be estimated for the diagnostic tests and treatments. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), discussions with individual hospitals and with the manufacturers of the comparators.

6. Equality issues

The National Institute for Health and Clinical Excellence (NICE) is committed to promoting equality and eliminating unlawful discrimination. NICE aims to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women, and
- eliminate unlawful discrimination on grounds of race, disability, age, sex and gender, sexual orientation, and religion or belief in the way we carry out our functions and in our employment policies and practices.

No potential equality issues have been identified in relation to this technology.

Appendix A Abbreviations

BAM: Bile acid malabsorption

BAS: Bile acid sequestrants

BSG: British Society of Gastroenterology

DAP: Diagnostics Assessment Programme

EAG: External Assessment Groups

IBD: Inflammatory bowel disease

IBS: Irritable bowel syndrome

IBS-D: Diarrhoea predominant inflammatory bowel disease

MTAC: Medical Technologies Advisory Committee

NHS: National Health Service

NICE: National Institute for Health and Clinical Excellence

QALY: Quality adjusted life year

Appendix B: References

- Färkkilä *et al.* (1996) Plasma lathosterol as a screening test for bile acid malabsorption due to ileal resection: correlation with 75SeHCAT test and faecal bile acid excretion. Clinical Science; 90(4):315-9.
- Galatola *et al*. (1992) The prevalence of bile acid malabsorption in irritable bowel syndrome and the effect of cholestyramine:an uncontrolled open multi-centre study. European Journal of Gastroenterology and Hepatology; 4:443-537
- Kurien *et al*. (2011) Bile acid malabsorption: An under-investigated differential diagnosis in patients presenting with diarrhoea predominant IBS type symptoms Scand. J. Gastro: (Abstract)
- Mowat *et al* (2011) Guidelines for the management of inflammatory bowel disease in adults. Gut; 60:571-607.
- NICE clinical guideline CG61 (2008) Irritable bowel syndrome: Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care. Available from: http://guidance.nice.org.uk/CG61
- Patient UK (2011)
- Pattni S and Walters J. (2009) Recent advances in the understanding of bile acid malabsorption: British Medical Bulletin. 92: 79-93
- Rubin *et al* (2000). Inflammatory Bowel Disease: epidemiology and management in an English general practice population. Aliment. harmacol. Ther.;14:1553-1559
- Sinha *et al* (1998). Idiopathic bile acid malabsorption: qualitative and quantitative clinical features and response to cholestyramine; 12: 839-844
- Smith *et al*. (2000) Bile acid malabsorption in persistent diarrhoea. Journal of Royal College of Physicians; 34(5): 448-51
- Thomas *et al*. (2003) Guidelines for the investigation of chronic diarrhoea 2nd edition. Gut; 52: 1-15
- Walters, JR (2010). Defining primary bile acid diarrhea: making the diagnosis and recognizing the disorder. Expert review of gastroenterology & hepatology 4 (5): 561–7.

- Wedlake *et al*. (2009) Systematic review: The prevalence of idiopathic bile acid malabosrption as diagnosed by SeHCAT scanning in patients with diarrhoea predominant IBS. Aliment Pharmacol Ther

Appendix C: Summary of product characteristics

Name of the medicinal product

SeHCAT 370 kBq capsules

Qualitative and Quantitative Composition

[^{75}Se]tauroselcholic acid is supplied as capsules of 370 kBq at the activity reference date.

Each capsule contains less than 0.1mg of tauroselcholic acid.

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.

This medicinal product contains:

Sodium: 71.04 mg in each capsule.

For a full list of excipients, see section 6.1.

Pharmaceutical Form

Capsule, hard.

Hard, gelatin capsule.

Clinical Particulars

Indications

[^{75}Se]tauroselcholic acid is used for the investigation of bile acid malabsorption and measurement of bile acid pool loss. It may be used in the assessment of ileal function, in the investigation of inflammatory bowel disease and chronic diarrhoea and in the study of entero-hepatic circulation.

Posology and method of administration

The normal dose for adults and the elderly is one capsule, administered orally.

If the product is to be administered to children the same dosage as in adults is used. There is no paediatric dosage form or clinical experience of the use of this product in children. A careful assessment of the risk/benefit ratio should be undertaken before use of the product in children, particularly since use of a fixed dose results in an increased effective dose equivalent in children (see section 11).

To ensure smooth passage of the capsule into the stomach, it is recommended that 15 ml drinks of water are taken by the patient before, during and after swallowing the capsule. The patient should be in a sitting or standing position during administration.

The instructions for preparation of radiopharmaceuticals are given in section 12.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Special warnings and precautions for use

The possibility of hypersensitivity should always be considered. Advanced life support facilities should be readily available.

Caution is advised in the administration of [^{75}Se]tauroselcholic acid to patients with severe hepatic dysfunction or biliary tract obstruction as in these conditions radiation dose to the liver will be significantly increased.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic or therapeutic result.

This medicinal product contains 71.04 mg sodium in each capsule. This needs to be taken into consideration for patients on a controlled sodium diet.

Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed and no interactions have been reported to date.

Fertility, pregnancy and lactation

Pregnancy:

No data are available on the use of this product in human pregnancy. Animal reproduction studies have not been performed.

When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation should be considered.

Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Only imperative investigations should be carried out during

pregnancy, when the likely benefit exceeds the risk incurred by the mother and the foetus.

Breast-feeding:

Before administering a radioactive medicinal product to a mother who is breast feeding consideration should be given as to whether the investigation could be reasonably delayed until after the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk.

If the administration is considered necessary, breast feeding should be interrupted. Breast milk should be expressed and discarded about three to four hours after [^{75}Se]tauroselcholic acid administration, after which breast feeding can be resumed.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Undesirable effects

The frequencies of undesirable effects are defined as follows:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data)

Immune system disorders

Not known: Hypersensitivity

Overdose

It is considered that overdosage is unlikely as the product is presented as a capsule which is administered orally in a controlled clinical setting. Should overdosage occur there are no known procedures which could be used to increase the clearance of activity from the body.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceuticals, hepatic and reticulo endothelial system, selenium (^{75}Se) tauroselcholic acid, ATC Code: V09DX01

At the chemical concentrations and activities used for diagnostic procedures [^{75}Se]tauroselcholic acid does not appear to exert any pharmacodynamic effects.

Pharmacokinetic properties

Tauroselcholic acid is a bile acid analogue which shows identical physiological behaviour with naturally occurring bile acid conjugates. Following oral administration in normal subjects, approximately 95% of the labelled bile acid is absorbed, mainly by the terminal ileum during each enterohepatic cycle. The distribution of activity is almost entirely confined to the lumen of the biliary ducts, gut and liver. Whole body retention data from normal subjects showed 97 to 100% of [^{75}Se]tauroselcholic was excreted with a biological half-life of 2.6 days and that, in most cases, a small component of about 3% was eliminated with a mean half time of 62 days.

Preclinical safety data

A single dose study in rats has indicated a safety margin of greater than 10,000 times the maximum human oral dosage. This agent is not intended for regular or continuous administration. Repeat dose toxicity studies, mutagenicity and long-term carcinogenicity studies have not been performed.

Pharmaceutical particulars

List of excipients

Disodium hydrogen phosphate dihydrate

Gelatin capsule

The gelatin capsule contains the following ingredients:

Titanium dioxide

Quinoline yellow

Erythrosine

Gelatin

Incompatibilities

Not applicable.

Shelf life

18 weeks from the date of manufacture. The activity reference date is 12 weeks before expiry.

Special precautions for storage

Store below 25°C. Do not freeze. Protect from light.

Store in accordance with national regulations for radioactive materials.

Nature and contents of container

SeHCAT is available in polystyrene containers with polythene caps. The capsules are held in place with polythene foam pads.

Pack size: single capsule packs.

Special precautions for disposal and other handling

Normal safety precautions for handling radioactive materials should be observed. After use, all materials associated with the preparation and administration of radiopharmaceuticals, including any unused product and its container, should be decontaminated or treated as radioactive waste and disposed of in accordance with the conditions specified by the local competent authority. Contaminated material must be disposed of in accordance with the conditions specified by the local competent authority. Contaminated material must be disposed of as radioactive waste via an authorised route.

Marketing Authorisation Holder

GE Healthcare Limited

Amersham Place

Little Chalfont

Buckinghamshire HP7 9NA

United Kingdom

Marketing Authorisation Number

PL 00221/0105

Date of First authorisation/Renewal of the authorisation

Date of first authorisation: 07 January 2002

Date of last renewal: 20 April 2006

Date of Revision of the text

01/2011

DOSIMETRY

The table below shows the dosimetry as calculated according to the Publication 80 of the ICRP (International Commission on Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press 1998).

Absorbed dose per unit activity administered (mGy/MBq)					
Organ	**Adult**	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	3.2E-01	4.1E-01	6.2E-01	9.4E-01	1.5E+00
Bladder	3.3E-01	4.2E-01	6.7E-01	1.0E+00	1.7E+00
Bone surfaces	2.3E-01	3.0E-01	4.3E-01	6.4E-01	1.2E+00
Brain	4.8E-02	5.6E-02	7.9E-02	1.2E-01	2.0E-01
Breast	7.7E-02	9.6E-02	1.8E-01	2.8E-01	5.2E-01
Gall bladder	6.4E+00	7.1E+00	9.0E+00	1.5E+01	4.8E+01
GI-tract					
Stomach	4.2E-01	5.5E-01	9.3E-01	1.5E+00	2.5E+00
SI	1.9E+00	2.4E+00	3.8E+00	5.9E+00	1.0E+01
Colon	2.0E+00	2.4E+00	3.8E+00	5.8E+00	1.0E+01
(ULI	1.9E+00	2.3E+00	3.5E+00	5.3E+00	9.1E+00)
(LLI	2.1E+00	2.6E+00	4.2E+00	6.5E+00	1.2E+01)
Heart	3.3E-01	4.3E-01	6.4E-01	9.6E-01	1.6E+00
Kidneys	5.0E-01	6.1E-01	8.9E-01	1.3E+00	2.0E+00
Liver	6.9E-01	8.7E-01	1.3E+00	1.8E+00	3.2E+00
Lungs	2.4E-01	3.3E-01	4.7E-01	7.2E-01	1.3E+00
Muscles	2.0E-01	2.5E-01	3.7E-01	5.5E-01	9.8E-01
Oesophagus	1.1E-01	1.4E-01	1.9E-01	2.9E-01	4.8E-01
Ovaries	1.0E+00	1.3E+00	2.0E+00	2.9E+00	4.9E+00
Pancreas	4.5E-01	5.8E-01	1.1E+00	1.7E+00	2.6E+00
Red marrow	2.9E-01	3.4E-01	4.6E-01	6.0E-01	8.3E-01
Skin	7.5E-02	9.1E-02	1.4E-01	2.2E-01	4.2E-01
Spleen	3.0E-01	4.1E-01	6.6E-01	1.0E+00	1.7E+00
Testes	9.2E-02	1.3E-01	2.2E-01	3.7E-01	7.0E-01
Thymus	1.1E-01	1.4E-01	1.9E-01	2.9E-01	4.8E-01
Thyroid	6.9E-02	9.6E-02	1.5E-01	2.7E-01	5.2E-01
Uterus	7.5E-01	9.4E-01	1.5E+00	2.3E+00	3.8E+00
Remaining Organs	2.6E-01	3.4E-01	5.3E-01	8.3E-01	1.3E+00
Effective dose (mSv/MBq)	**6.9E-01**	**8.6E-01**	**1.3E+00**	**2.0E+00**	**3.9E+00**

For this product the effective dose to a healthy adult resulting from the administration of a 370 kBq capsule is typically 0.26 mSv.

In most clinical investigations for which this substance is used (e.g. Crohn's disease) the effects of impaired ileal absorption and shorter gastrointestinal transit time tend to reduce the dose commitment compared with the normal case. However, in patients with severe cholestatic jaundice, the liver dose has been estimated to be about 100 times the normal value.

INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisations (see section 6.6).

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

PROCEDURE FOR USE

Measurement of bile pool loss

Measurement of the rate of bile loss from the endogenous pool using SeHCAT may be achieved either by determining the retention of activity in the body over a period of days or by determining the excretion of activity in faeces. The results may be expressed as a rate of loss if several measurements are taken, or more simply as a retained percentage after a fixed period (7 days is convenient). A whole body counter or other counter or other counting techniques may be used.

For some investigations scintigraphic studies may be appropriate.

Measurement of retained activity

Whole body counter

A 370 kBq (10 µCi) capsule is administered to the patient together with a drink of water. Using conventional whole body counting techniques an initial count of the patient provides, after background subtraction, a zero- time or 100% value.

After 7 days the patient is counted again, and the retained activity expressed as a percentage of the original value.

Alternative techniques

If a whole body counter is not available, other counting techniques may be used successfully. Since the activity is confined to the abdominal region, a counter with a field of view encompassing the abdomen can be employed. A gamma camera with its collimator removed has proved successful and single crystal probes have also been used.

It is important to keep the positioning of the patient and counter constant at each measurement. To minimise the effect of geometric variations, the counting head should be arranged at the maximum height above the patient couch.

A standard axial positioning of the patient along the centreline of the counter should be maintained. The centre of the crystal should be positioned midway between the umbilicus and the base of the sternum.

To avoid excessive background interference from sources of technetium-99m, it is recommended that the camera window be set at the 289 keV photon peak of selenium-75 (20% window).

If an uncollimated gamma camera is being used, normal gamma camera procedures for spectrum stabilisation and uniformity checking with flood sources should be observed. If the patient is the subject of other simultaneous radionuclide studies, check that the interference from other photon peaks is eliminated or make allowances in the procedure to compensate for the excessive count rate.

Procedure

1. The patient should be given at least 15 ml of water to drink prior to taking the capsule. A similar drink of water should be taken with the capsule and again afterwards to encourage rapid transit of the capsule to the stomach and subsequent dispersion of the contents.
2. Allow 3 hours for physiological equilibration.
3. Measure the background twice, setting the camera window as described above. A preset count or time may be used.
4. Place the patient on the couch as described above. Count for pre- set time (300 seconds suggested and record the counts).
5. Turn the patient and repeat the count from the other view.
6. Measure the background again.
7. After background subtraction, calculate the geometric mean of the two patient counts $\sqrt{(PA \times AP)}$.
8. Repeat steps 3-7 after 7 days.
9. Correct the day 7 value for radioactive decay by multiplying by 1.04
10. Express day 7 value as percentage of day 0 value.

Measurement of excreted activity

The alternative method of estimating bile acid loss is by scintillation counting of total faecal samples collected over a period (e.g. 7 days). A dosage of 370 kBq (10 µCi) (orange and yellow capsule) is recommended. It is important to ensure that standard geometry is monitored and that total collection of faeces is achieved. Samples from patients undergoing two simultaneous radionuclide investigations should not be counted unless faecal excretion of the other radionuclide is known to be insignificant, or unless the counting equipment can be selectively set to accumulate only selenium-75 photon emissions.

Counting of the faecal γ activity using a sodium iodide crystal detector in a well counter or other suitable instrument is the counting method of choice.

The procedure for the administration of the capsule of SeHCAT is the same as when measuring retained activity.