

# SeHCAT [tauroselcholic (selenium-75) acid] for the investigation of bile acid malabsorption and measurement of bile acid pool loss: a systematic review and cost-effectiveness analysis

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## Scientific summary

Investigation of bile acid malabsorption and measurement of bile acid pool loss

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# Scientific summary

## Background

The principal diagnosis/indication for this assessment is chronic diarrhoea due to bile acid malabsorption (BAM). BAM is one of several causes of chronic diarrhoea 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.

Selenium-75-homocholeic acid taurine (SeHCAT; GE Healthcare) is a radiopharmaceutical that is licensed for use in the investigation of BAM and measurement of bile acid pool loss. 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 [National Institute for Health and Care Excellence (NICE). *Diagnostics Assessment Programme: SeHCAT (Tauroselcholic [75Selenium] acid) for the investigation of diarrhoea due to bile acid malabsorption: final scope*. London: NICE; 2011]. The main comparator for the assessment includes tests and clinical observations contained in the British Society of Gastroenterology (BSG) guidelines for the investigation of chronic diarrhoea. As mentioned in the NICE scope, there is no direct comparator for SeHCAT.

In consultation with NICE and clinical experts during early scoping it was agreed that the review should focus on two populations:

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).

## Objectives

To evaluate the clinical effectiveness and cost-effectiveness of selenium-75-homocholeic acid taurine (SeHCAT), a bile acid analogue that is used as a test for investigating BAM and the measurement of bile acid pool loss in patients referred to a gastrointestinal clinic for investigation and diagnosis of BAM.

This can be translated into the following research questions. For people with chronic diarrhoea with unknown cause and in people with Crohn's disease and chronic diarrhoea with unknown cause (i.e. before resection):

1. What are the effects of SeHCAT compared with no SeHCAT in terms of chronic diarrhoea, other health outcomes and costs?
2. What are the effects of bile acid sequestrants (BASs) compared with no BASs in people with a positive or negative SeHCAT test?
3. Does a positive or negative SeHCAT test predict improvement in terms of chronic diarrhoea, other health outcomes and costs?

## Methods

A systematic review was conducted to summarise the evidence on the clinical effectiveness of SeHCAT for the assessment of BAM and the measurement of bile acid pool loss. Search strategies were based on target condition and intervention. Nine databases were searched up to April 2012:

- MEDLINE (1946–week 1 April 2012) (OvidSP)
- MEDLINE In-Process & Other Non-Indexed Citations and Daily Update (inception up to 17 April 2012) (OvidSP)
- EMBASE (1980–week 15 2012) (OvidSP)
- Cochrane Database of Systematic Reviews (The Cochrane Library Issue 3:2012) (Wiley Online Library)
- Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 4:2012) (Wiley Online Library)
- Database of Abstracts of Reviews of Effects (inception up to 19 April 2012) [Centre for Reviews and Dissemination (CRD) website]
- Health Technology Assessment (HTA) Database (inception up to 19 April 2012) (CRD website)
- Science Citation Index (1970–18 April 2012) (Web of Science)
- National Institute for Health Research HTA (inception up to 19 April 2012) (internet).

Research registers and conference proceedings were also searched. Systematic review methods followed the principles outlined in the CRD guidance for undertaking reviews in health care and the NICE Diagnostic Assessment Programme interim methods statement.

The methodological quality of included studies was assessed using standard tools.

Results were summarised in tables and text, stratified by principal diagnosis (chronic diarrhoea/IBS or Crohn's disease), as appropriate. The review included only three assessments of the relationship between the SeHCAT test and treatment with BAS (cholestyramine). These three studies used different SeHCAT cut-off points to define BAM and pooling of results was deemed inappropriate.

In the health economic analysis, the cost-effectiveness of SeHCAT for the assessment of BAM in patients with chronic diarrhoea was estimated in two different populations. The first is the population of patients with chronic diarrhoea with unknown cause and symptoms suggestive of diarrhoea-predominant irritable bowel syndrome (IBS-D) and the second population concerns patients with Crohn's disease without ileal resection with chronic diarrhoea.

For both populations the cost-effectiveness of SeHCAT compared with no SeHCAT was assessed. For the SeHCAT option we defined various strategies based on the test cut-off points used to classify patients. For the IBS-D patient population, data were available to be able to distinguish between cut-off points of 5%, 10% and 15%. For the Crohn's patient population, only data on a 10% and 15% SeHCAT test cut-off were available. For the no SeHCAT strategy all patients receive regular treatment for either IBS-D or chronic diarrhoea in Crohn's. Additionally, in the scoping document, 'trial of treatment with BAS' was mentioned as another possible strategy without specifically including it as a comparator. According to the clinical experts at the scoping meeting, trial of treatment is rarely used as a treatment strategy and was thus not considered relevant. However, trial of treatment could also not be completely excluded as an option. Thus, in this report, for both populations we present two sets of results: one where trial of treatment is not considered as a comparator and one where it is. In the trial of treatment strategy, patients first receive a BAS and when patients do not respond they receive regular treatment for either IBS-D or chronic diarrhoea in Crohn's.

For each population, three models were combined:

1. a short-term decision tree that models the diagnostic pathway and initial response to treatment (first 6 months)
2. a long-term Markov model that estimates the lifetime costs and effects for patients initially receiving BAS
3. a long-term Markov model that estimates the lifetime costs and effects for patients initially receiving regular treatment (IBS-D treatment in the first population and Crohn's treatment in the second population).

In the decision tree the 6-month number of responders and the expected costs were calculated for each comparator while for the Markov models lifetime expected quality-adjusted life-years (QALYs) and expected costs per patient were calculated for each comparator.

Where possible, input for the model was based on our SeHCAT systematic review, other published literature and UK databases. When such evidence was not available, expert opinion was used. The impact of uncertainty about the various input parameters on the outcomes was explored through probabilistic sensitivity analyses and scenario analyses.

Incremental cost-effectiveness ratios (ICERs) were estimated as additional cost per additional responder in the short term (first 6 months) and per additional QALY in the long term (lifetime).

## Results

Twenty of the 21 studies included studies in the systematic review were studies assessing the value of SeHCAT in predicting the response to BAS. Of these 20 SeHCAT studies, 19 included people with chronic diarrhoea with unknown cause and two studies included people with Crohn's disease and chronic diarrhoea.

Three studies were reasonably reliable in assessing the relationship between the SeHCAT test and response to treatment with cholestyramine. However, the studies had small numbers of patients with unknown cause chronic diarrhoea, they used different cut-offs for the assessment of BAM and between study heterogeneity was considerable.

None of the studies looking specifically at people with Crohn's disease presented reliable data for the prediction of response to treatment with BAS because no data were presented for people with a negative SeHCAT test in the two studies.

One randomised controlled trial in patients with IBS-D, which compared treatment with BAS (colesevelam) with placebo, showed no significant differences in terms of colonic transit, bowel function or adverse events. However, randomisation (sequence generation and allocation concealment) was not adequately reported and groups were small ( $n = 12$  in both arms).

For people with chronic diarrhoea, 19 studies provide data on the effectiveness of BAS given a positive SeHCAT test; three studies also provided data on the effectiveness of BAS given a negative SeHCAT test. For those with a positive SeHCAT test response rates were on average 85%, 73% and 72% for cut-offs at 5%, 10% and 15%, respectively. For those with a negative SeHCAT test the response rate was 14% at a cut-off of 5% and 0% at a cut-off of 15%. For people with Crohn's disease and a positive SeHCAT test the response rate was 95% at a cut-off of 5% and 86% or 89% at a cut-off of 15%.

The health economic analysis showed for the IBS-D population that for the short term (first 6 months), when trial of treatment is not considered as a comparator, that the optimal choice depends on the

willingness to pay for an additional responder. For lower values (base case £2400, scenarios between £1800 and £4600) the choice will be no SeHCAT in all scenarios; for higher values either SeHCAT 10% or SeHCAT 15% becomes cost-effective.

For the lifetime perspective, we did not define a base case, as we had no information of any kind to inform the transition probabilities between the health states diarrhoea and no diarrhoea and vice versa. Thus, only scenario analysis was performed. The various scenarios showed widely differing results. Depending on the scenario, in the threshold range of £20,000 to £30,000 per QALY gained, we found as optimal choice either no SeHCAT, SeHCAT 5% or SeHCAT 15%; only SeHCAT 10% never had the highest probability of being cost-effective.

When trial of treatment is considered a comparator, the analysis showed for the IBS-D population that for the short term, trial of treatment is the optimal choice across a range of scenarios. In the base-case scenario, trial of treatment dominated all other strategies and had a 95% probability of being the most cost-effective option. In the various scenarios, trial of treatment was dominant compared with all strategies. For all scenarios trial of treatment had the highest probability of being cost-effective; this probability was for most scenarios around 90%, decreasing for some scenarios to 50%.

For the lifetime perspective, for all but two scenarios, trial of treatment was the strategy with the highest probability of being cost-effective for thresholds above £5000–15,000, with no SeHCAT the most favourable strategy for lower-threshold ICERs. In the two scenarios where the transition probability from diarrhoea to no diarrhoea in the BAM model was 5% per cycle while all others were 0, we observed that for thresholds > £15,000 SeHCAT 15% had the highest probability of being cost-effective.

For the Crohn's population, the short-term evaluation without trial of treatment as comparator showed for the short term that the optimal choice depends on the willingness to pay for an additional responder. For lower values (base case £2300, scenarios between £1500 and £4000) the choice will be no SeHCAT in all scenarios; for higher values SeHCAT 10% becomes cost-effective.

For the long term, the various scenarios show widely differing results. Depending on the scenario, in the threshold range of £20,000–30,000 per QALY gained, we found as optimal choice either no SeHCAT or SeHCAT 15% while some scenarios found that all three strategies had the same probability of being cost-effective.

When trial of treatment is considered a comparator, the analysis showed for the Crohn's population that for the short term, trial of treatment dominated all other strategies (in terms of number of responders) and had an almost 100% probability of being the most cost-effective option. In the various scenarios, trial of treatment was dominant compared with all strategies. For all scenarios trial of treatment had the highest probability of being cost-effective; for most scenarios this probability was around 90%.

For the lifetime perspective in Crohn's with trial of treatment, again the various scenarios show widely differing results. Depending on the scenario, in the threshold range of £20,000–30,000 per QALY gained, we found as optimal choice either trial of treatment, no SeHCAT or SeHCAT 15%.

## Conclusions

We found three studies assessing the relationship between the SeHCAT test and response to treatment with cholestyramine. However, the studies had small numbers of patients with unknown cause chronic diarrhoea, and they used different cut-offs to define BAM. None of the studies looking specifically at people with Crohn's disease presented reliable data for the prediction of response to treatment with BAS because no data were presented for people with a negative SeHCAT test in the two studies.

One randomised controlled trial in patients with IBS-D, which compared treatment with BAS (colesevelam) with placebo, showed no significant differences in terms of colonic transit or adverse events.

The health economic analysis has shown similar results for both patient populations considered.

For the short term (first 6 months), when trial of treatment is not considered as a comparator, the optimal choice depends on the willingness to pay for an additional responder. For lower values (between £1500 and £4600) the choice will be no SeHCAT in all scenarios; for higher values either SeHCAT 10% or SeHCAT 15% becomes cost-effective.

For the lifetime perspective, the various scenarios showed widely differing results: in the threshold range of £20,000 to £30,000 per QALY gained we found as optimal choice either no SeHCAT, SeHCAT 5% (only IBS-D) or SeHCAT 15%.

When trial of treatment is considered a comparator, the analysis showed that for the short term, trial of treatment is the optimal choice across a range of scenarios.

For the lifetime perspective with trial of treatment, again the various scenarios show widely differing results. Depending on the scenario, in the threshold range of £20,000–30,000 per QALY gained, we found as optimal choice either trial of treatment, no SeHCAT or SeHCAT 15%.

In conclusion, the various analyses have shown that for both populations considerable decision uncertainty exists, and that no firm conclusions can be formulated about which strategy is optimal.

### *Suggested research priorities*

Standardisation of the definition of a positive SeHCAT test should be the first step in assessing the usefulness of this test. As there is no reference standard for the diagnosis of BAM and SeHCAT testing provides a continuous measure of metabolic function, diagnostic test accuracy (DTA) studies are not the most appropriate study design. However, in studies where all patients are tested with SeHCAT and all patients are treated with BAS, response to treatment can provide a surrogate reference standard; further DTA studies of this type may provide information on the ability of SeHCAT to predict response to BAS. A potentially more informative option would be multivariate regression modelling of treatment response (dependent variable), with SeHCAT result and other candidate clinical predictors as covariates. Such a study design could also inform the definition of a positive SeHCAT result.

The limited evidence identified means that the effectiveness of BAS, both in unselected patients with chronic diarrhoea and where treatment decisions are based on SeHCAT test results, remains uncertain. Two possible randomised controlled designs are, therefore, potentially useful:

1. Patients with chronic diarrhoea receive SeHCAT testing and all patients are then randomised to treatment with BAS or placebo. This study design can provide information on the effectiveness of BAS in all patients with relevant symptoms. If the analysis is then stratified by test result, information can be obtained on any difference in effectiveness between SeHCAT-positive and SeHCAT-negative patients, or variation in the effectiveness of BAS with levels of SeHCAT absorption.
2. Patients with chronic diarrhoea receive SeHCAT testing and only patients with a positive SeHCAT test are randomised to treatment with BAS or placebo. This study design can provide information on the effectiveness of BAS in SeHCAT-positive patients. This design might be considered more ethical if it is believed that current evidence is sufficient to indicate no or minimal effectiveness of BAS in SeHCAT-negative patients.

The inclusion criteria for such a trial are important to make sure that patients are not unnecessarily subjected to BAS treatment and at the same time, all patients suitable for a SeHCAT test are included. Treatment strategies should be clearly described in the study protocol. Long-term follow-up is needed to

fully assess the effectiveness of BAS in all relevant patient groups. Outcomes should include all relevant bowel function and transit outcomes, as well as quality of life (including utility) and adverse events of testing and treatment. Additionally, such trials should enable the collection of resource use data related to the chronic diarrhoea problems.

Moreover, the large variation in outcomes between the scenarios considered for the Markov models make it clear that long-term data are important for patients with IBS-D, patients identified as having BAM and Crohn's patients with chronic diarrhoea. These data do not necessarily need to come from a randomised controlled trial; it might be possible to set up a retrospective study using existing databases, patient records, etc., to find relevant long-term data. If those sources of information do not provide enough information, prospective observational studies could collect data on treatment and treatment switches and resource use.

It was also shown in the various scenarios that the assumption about utility values for BAM health states have an important impact on the results. For reliable utility estimates for the various health states, a cross-sectional study in the relevant patient populations would be a relatively easy way to inform these important parameters.

## Study registration

This study is registered as PROSPERO CRD42012001911.

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