PRODUCT MONOGRAPH

SeHCAT
(Tauroselcholic Acid)

370 kBq Capsules

Radiodiagnostic Agent

(Measurement of Bile Acid Pool Loss)

GE Healthcare Canada Inc.
2300 Meadowvale Blvd.,
Mississauga, Ontario
L5N 5P9

Control #: 195675 **Date of Approval: September 7, 2016**

NAME OF DRUG

SeHCAT

(tauro-23 (^{75} Se) selena-25 homocholic acid)

THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION

Radiodiagnostic Agent

(Measurement of Bile Acid Pool Loss)

DESCRIPTION

SeHCAT is supplied as capsules in single capsule packs.

Orange and yellow capsules each containing:

Tauroselcholic acid (^{75}Se) 370 kBq (10μCi) ±10%

The weight of active ingredient is less than 0.1 mg per capsule. It is absorbed on inert carrier (disodium phosphate dihydrate, approximately 275 mg per capsule).

Physical Characteristics of ^{75}Se

Table 1. Principal Radiation Emission Data

Selenium-75 has a half life of 120 days. It decays by 100% electron capture to stable arsenic, emitting a number of γ -rays as indicated below:

Energy MeV	Emitted %	Internally Converted %
0.024	0.03	5.5
0.066	1.1	0.3
0.097	2.9	3.0
0.121	15.7	0.7
0.136	54.0	1.6
0.199	1.5	---
0.266	56.9	0.4
0.280	23.9	0.2
0.304	1.2	0.1
0.401	11.7	---

External Radiation

The exposure rate in air at 1m from a point source of 37 MBq (1 mCi) is 0.2 mR/h. The specific gamma ray constant for Selenium-75 (including associated X-ray emission) is 0.17 R/MBq hour (6.3 R/mCi-hour) at 1 cm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in Table 2.

Table 2 Radiation Attenuation by Lead Shielding

Shield Thickness (mm of lead)	Coefficient of Attenuation
0.008	0.5
2.2	10^{-1}
8.6	10^{-2}
16.0	10^{-3}
25.0	10^{-4}
35.0	10^{-5}

To correct for physical decay of this radionuclide the fractions that remain at selected intervals of time of reference are shown in Table 3.

Table 3. Physical Decay Chart: Selenium-75, Half-Life 120 Days

Week	Orange/ Yellow Capsule	
	kBq	μCi
-4	435.0	11.76
-3	417.7	11.29
-2	401.2	10.84
-1	385.3	10.41
0(ref'nc)	370.0	10.00
+1	355.3	9.60
+2	341.3	9.22
+3	327.7	8.86
+4	314.7	8.51
+6	290.3	7.85
+8	267.7	7.24
+10	246.9	6.68
+12 (expiry)	227.7	6.16

CLINICAL PHARMACOLOGY

Tauroselcholic acid (Tauro-23 (^{75}Se) selena-25 homocholic acid) does not occur naturally. However, it is an analogue of the naturally occurring bile acid conjugate taurocholic acid. Studies have shown identical physiological behaviour between the two compounds ([4,5]).

Endogenous bile acids are formed in the liver, secreted into bile and reabsorbed by an active transport mechanism across the ileal mucosa. They are also reabsorbed by passive diffusion in the proximal small intestine and colon. Conjugation with either glycine or taurine is believed to be complete when the bile acids leave the hepatocytes ([6]) but a degree of deconjugation by intestinal micro-organisms does occur.

The taurine conjugate appears to be more resistant to deconjugation than the glycine equivalent ([7]). The conjugated bile acids are much more slowly reabsorbed by the passive mechanism ([6]) and are mainly reabsorbed by the ileum.

Comparative studies with ^{14}C-taurocholic acid have shown SeHCAT to be significantly more resistant to bacterial dehydroxylation and deconjugation by mixed fecal anaerobic organisms ([8]). Excision or by-pass of the terminal ileum abolishes absorption of SeHCAT ([5]). Thus SeHCAT can be considered to be specifically absorbed by the active mechanism of the ileum. After oral administration of a capsule, SeHCAT becomes mixed with the endogenous bile acid pool.

INDICATIONS AND USAGE

SeHCAT provides a means for measuring the rate of bile acid loss from the endogenous pool. This can be achieved by determining either the excretion of activity in feces or the retention of activity in the body over a period of days. This is useful in the assessment of

ileal involvement in, for example, Crohn's disease ([1]), in assessing reduction of ileal absorptive function following certain surgical interventions ([1,2,3]) and in assisting in the classification of patients suffering from chronic diarrhea ([1,2,3,4]). 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).

The biological half-life of taurocholic acid has been measured by determination of the fecal excretion rate of ^{14}C-taurocholic acid ([9]). Results obtained for SeHCAT are in good agreement with this value. A lower limit of retention at 7 days of 19% for normals ([1]) compares with a value of 20% from the work with ^{14}C-taurocholic acid, although this will depend to a degree on the local population where dietary and bowel habits may lead to slightly different values.

Since SeHCAT is specifically absorbed by the ileum, the extent of loss of ileal bile acid absorptive function in, for example, cases of suspected Crohn's Disease can be determined.

A major symptom of bile acid malabsorption is chronic diarrhea (cholegenic diarrhea) due to the inhibitory effect of bile acids on colonic absorption ([10]). This may be treated by oral administration of cholestyramine, an insoluble bile acid binding resin ([3]). Chronic diarrhea can also arise from other causes; for example, ulcerative colitis or infections of the small intestine. SeHCAT can therefore be used in assisting the classification of patients presenting with chronic diarrhea ([2,3,4]).

The clinical performance of SeHCAT has been compared with another method of assessing bile acid malabsorption, the ^{14}C-glycocholate breath test ([2]). Results indicate

that the SeHCAT test compares favourably with the older method and is more sensitive for the detection of bile acid malabsorption ([3]).

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients

WARNINGS

Radiopharmaceuticals should be used only by or under the control of physicians who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

Since adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this radiopharmaceutical preparation should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards.

Where an assessment of the risk/ benefits ratio suggests use of this product in lactating mothers, nursing should be stopped.

Adequate studies do not exist to support the use in children. As in pregnancy and lactating mothers, the benefit to risk ratio should be assessed before consideration is given to the use of this product in this age group.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability should be performed during the first few (approximately 10 days) following the onset of menses.

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

PRECAUTIONS

As in the use of any other radioactive material, care should be taken to insure minimal radiation exposure to the patient, consistent with proper patient management and to ensure minimum exposure to occupational workers.

The sodium content of SeHCAT of about 71 mg per capsule needs to be taken into consideration for patients on a controlled sodium diet.

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.

ADVERSE REACTIONS

Immune system disorders: Hypersensitivity

DOSAGE AND ADMINISTRATION

The adult dose is one capsule administered orally for a single diagnostic procedure.

To ensure smooth passage of the capsule into the stomach, it is recommended that a 15ml drink of water is taken by the patient both before, during and after swallowing the capsule. The patient should be in a sitting or standing position during administration (^{11}).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

RADIATION DOSIMETRY

Radiation doses have been calculated using MIRD tables and formulae together with data from measurements of whole-body distribution and from long-term whole-body counting in rats, mice and man (^{14}). The estimated absorbed radiation dose to an average adult 70 kg patient is shown in Table 4.

Table 4. Absorbed Radiation Doses

	Normal Health		No Gall Bladder		Severe Jaundice	
	µGy/ kBq	m rad/ µCi	µGy/ kBq	m rad/ µCi	µGy/ kBq	m rad/ µCi
Liver	0.4	1.4	0.4	1.3	55.1	204
Gall Bladder	3.2	12.0	---	---	11.3	42
Small Intestine	3.0	11.0	3.5	13.0	5.9	22
Upper Large Intestine	2.2	8.2	2.5	9.2	7.3	27
Lower Large Intestine	2.2	8.1	2.3	8.4	3.5	13
Ovaries	1.1	4.1	1.2	4.5	3.8	14
Total Body	0.3	1.0	0.3	1.0	5.7	21

MEASUREMENT OF RETAINED ACTIVITY

A. Whole Body Counter

This measurement can be obtained by use of a whole body counter ([1,5]) in a manner similar to that employed for measurement of B_{12} absorption/ retention using ^{58}Co labelled cyanocobalamin ([12]).

A 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.

B. 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 ([2]) and single crystal probes have also been used.

In either case a 370 kBq (10μCi) (orange and yellow) capsule is suitable.

It is important to keep the positioning of the patient and counter constant at each measurement. To minimize 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 ^{99}Tc, it is recommended that the camera window be set at the 280 keV photon peak of ^{75}Se (20% window).

If an uncollimated gamma camera is being used, normal gamma camera procedures for spectrum stabilization and uniformity checking with flood sources should be observed.

If the patient is the subject of other radionuclide studies, check that the interference from other photon peaks is eliminated or make allowances in the procedure to compensate for excessive count rate.

Procedure

1. The patient should be given at least 15ml of water to drink prior to taking the capsule. A similar drink of water should be taken with the capsule and 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 a preset 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 x AP).
8. Repeat steps 3-7 after 7 days.
9. Correct the 7 day 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 fecal samples collected over a period (eg; 7 days). A dosage of 370 kBq (10μCi) (orange and yellow capsule) is recommended. It is important to ensure a standard geometry is maintained and that total collection of feces is achieved. Samples from patients undergoing simultaneous radionuclide investigations should not be counted unless fecal excretion of other radionuclide is known to be insignificant, or unless the counting equipment can be selectively set to accumulate only ^{75}Se photon emissions.

Counting of fecal activity by sodium iodide crystal detector in a well counter or other suitable instrument is much more accurate and convenient than methods employed formerly, ie; conventional chemical analysis for bile salt content or liquid scintillation counting following administration of ^{14}C or ^{3}H labelled bile acids.

SCINTIGRAPHIC STUDIES

SeHCAT has been used in scintigraphic studies of the enterohepatic circulation ([13]). Transit times between stomach and gall bladder may be measured on the day of administration. A dosage of 370 kBq (10μCi) (orange and yellow capsule) is recommended.

On subsequent days the fasting distribution of the bile acid pool and the gall bladder to gall bladder transit time can be determined by imaging the patient in the fasting state and then stimulating contraction of the gall bladder using either a suitable meal of CCK (cholecystokinin) injection.

HOW SUPPLIED

SeHCAT is supplied in single capsule packs.

Orange and yellow capsules contain 370kBq (10 μCi)

The activity is absorbed on an inert carrier.

STORAGE

Store at room temperature.

AVAILABILITY

From stock.

EXPIRY

The capsules should not be used later than 12 weeks after the reference date.

REFERENCES

1. Nyhlin, H., Merrick, M.V., Eastwood, M.A. and Bryden, W.G. Evaluation of ileal function using SeHCAT, a gamma labelled conjugated bile acid. An initial assessment. Gastroenterology, vol. 84, pp. 63-68, 1983.

2. Hess Thaysen, E., Orholm, M., Arnfred, T., Carl, J., and Rodbro, P. Assessment of Ileal function by abdominal counting of the retention of a gamma emitting bile acid analogue. Gut, vol. 23, pp.862-865, 1982.

3. Hess Thaysen, E., Orholm, M., Arnfred, T., Carl, J., and Rodbro P. Ileal bile acid conservation assessed by abdominal gamma camera counting. A preliminary investigation. Stockholm World Congress in Gastroenterology, June 1982.

4. Delhez, H., Van Den Berg, J.W.O., Van Blankenstein, M., and Meerwaldt, J.H. New method for the determination of bile acid turnover using ^{75}Se-homocholic acid taurine. European Journal of Nuclear Medicine, Vol. 7, pp. 269-271, 1982.

5. Merrick, M.V., Eastwood, M.A., Anderson, J.R. and Ross, H.M., Enterohepatic circulation in man of a gamma-emitting bile-acid conjugate, 23-Selena-25-Homotauro cholic acid (SeHCAT). Journal of Nuclear Medicine, Vol. 23, pp. 126-130, 1982.

6. Hofmann, A.F.The enterohepatic circulation of bile acids in man. Clinics in Gastroenterology, vol. 6(1), pp. 3-24, 1977.

7. Hepner, G.W., Sturman, J.A., Hofmann, A.F. and Thomas, P.J. Metabolism of steroid and amino acid moieties of conjugated bile acids in man III cholyl taurine. Journal of Clinical Investigation, vol. 52, pp. 433-440, 1973.

8. UK Patent Application No. 2.028.333

9. Van Blankenstein, M., Hoyset, T., Horchner, P., Frenkel, H. And Wilson, J.H.P. Faecal bile acid radioactivity, a sensitive and relatively simple test for ileal dysfunction. Netherlands Journal of Medicine, vol. 20, pp. 248-252, 1977.

10. Heaton, K.W. Disturbances of bile acid metabolism in intestinal disease. Clinics in Gastroenterology, vol. 6(1), pp. 69-89, 1977.

11. Fisher, R.S., Malmud, L.S., Applegate, G., Rock, E., and Lorber, S.H. Effect of bolus composites on esophageal transit. Journal of Nuclear Medicine, vol. 23, pp. 878-882, 1982.

12. Warner, G.T. and Oliver, R. A whole-body counter for clinical measurements utilizing the 'Shadow Shield' technique. Physics in Medicine and Biology, vol. 11(1), pp. 83-94, 1966.

13. Meller, S.T. Kupfer, R.M., Jazwari, R.P., Payne, J.H., McCready, V.R. and Northfield, T.C. Radionuclides in Gastroenterology. Proceedings of British Institute of Radiology, vol. 54(644), pp. 703-704, 1981.

14. Soundy, R.G., Simpson, J.D., Ross, H.McL.. and Merrick, M.V. Absorbed dose to man from the Se-75 labelled conjugated bile salt SeHCAT: Concise communication. Journal of Nuclear Medicine, vol. 23, pp. 157-161, 1982.