HICON™
Kit for the Preparation of Sodium Iodide I 131 Capsules and Solution USP Therapeutic - Oral

DESCRIPTION

HICON™ is a kit which provides a solution of Sodium Iodide I-131 with a radioconcentration of 37 gigabecquerels/mL (1,000 millicuries/mL). Each mL of the concentrated solution contains 37 GBq of no-carrier-added Sodium Iodide I-131, <2 mg of Disodium Edetate Dihydrate USP as a stabilizer, <4.4 mg of Sodium Thiosulfate Pentahydrate USP as a reducing agent, and <40 mg of Dibasic Sodium Phosphate Anhydrous USP. The pH of the solution is between 7.5 and 9.0.

The concentrated solution provided with HICON™ is intended for use in the preparation of capsules and solution of varying strengths for oral administration for therapy.

Sodium Iodide I 131 Solution USP is designated chemically as Na ^{131}I (MW 153.99, CAS 7681-72-5).

Hard gelatin capsules provided for the preparation of the Sodium Iodide I-131 final dosage form contain approximately 300 mg of Dibasic Sodium Phosphate Anhydrous USP as the absorbing buffer.

PHYSICAL CHARACTERISTICS

Iodine I-131 decays by beta emission and associated gamma emission with a physical half-life of 8.04 days.[1] Photons that are useful for detection and imaging are listed in Table 1.

Table 1
Principal Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Beta-4 (average)	89.3	191.6
Gamma-14	81.2	364.5

[1]Kocher, David C., "Radioactive Decay Data Tables", DOE/TIC-11026, (1981) p. 133.

EXTERNAL RADIATION

The specific gamma-ray constant for iodine I-131 is 15.8 $\mu C \cdot kg^{-1} \cdot MBq^{-1} \cdot hr^{-1}$ (2.2 R/mCi-hr) at 1 cm. The first half-value thickness of lead (Pb) for iodine I-131 is 0.24 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. For example, the use of 2.55 cm of Pb will decrease the external radiation exposure by a factor of about 1,000.

Table 2
Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) cm	Coefficient of Attenuation
0.24	0.5
0.89	10^{-1}
1.6	10^{-2}
2.55	10^{-3}
3.73	10^{-4}

To correct for physical decay of iodine I-131, the fractions that remain at selected intervals after the time of calibration are shown in Table 3.

Table 3
Physical Decay Chart: Iodine I-131, Half-Life 8.04 Days

Days	Fraction Remaining	Days	Fraction Remaining	Days	Fraction Remaining
0*	1.000	11	.388	22	.151
1	.918	12	.356	23	.138
2	.842	13	.327	24	.127
3	.773	14	.300	25	.116
4	.709	15	.275	26	.107
5	.651	16	.253	27	.098
6	.597	17	.232	28	.090
7	.548	18	.213	29	.083
8	.503	19	.195	30	.076
9	.461	20	.179		
10	.423	21	.164		

*Calibration time

CLINICAL PHARAMACOLOGY

Pharmacokinetics

Absorption: Following oral administration, Sodium Iodide I-131 is readily absorbed from the gastrointestinal tract.

Distribution: Following absorption, the iodide is primarily distributed within the extra-cellular fluid of the body. It is trapped by the thyroid. The thyroid uptake of iodide is usually increased in hyperthyroidism and in goiter with impaired hormone synthesis, decreased in hypothyroidism, and normal to decreased in hypothyroidism receiving iodine. It should be noted that the uptake of radioactive iodide is a function of stable iodide concentration in the serum and the functional state of the thyroid. The iodine concentrating mechanism of the thyroid, termed the iodide trap or pump, accounts for an iodide concentration of some 25 times plasma levels, but may increase as much as 500 times under certain conditions. It is also concentrated by the stomach, choroid plexus, and salivary glands, but is not protein-bound.

Metabolism: Trapped iodide is oxidized to iodine and organically incorporated so rapidly that the iodide trap of the thyroid contains less than 0.2% free iodide in comparison to the organically bound iodine. This process results in further concentration of iodine in the thyroid gland to about 500 times that in the blood.

The iodinated organic compounds chiefly consist of thyroxine (T4) and triiodothyronine (T3), which are bound by thyroglobulin in the follicular colloid. T4 and T3 are released by enzymatic proteolysis of thyroglobulin into the blood where they are specifically bound and transported by plasma thyroid binding proteins. These reactions are primarily under the control of anterior pituitary gland release of thyroid stimulating hormone (TSH) and hypothalamic thyroid release factor (TRF).

Excretion: Sodium Iodide I-131 is excreted by the kidneys. The normal range of urinary excretion is 37-75% of the administered dose, varying with the thyroid and renal function of the patient.

Pharmacodynamics

Stimulation of radioiodide uptake may be achieved by the administration of thyrotropin or placing the patient on a low iodine diet prior to treatment. Palliative effects may be seen in patients with papillary and/or follicular carcinoma of the thyroid. Radioiodide will not be taken up by giant cell and spindle cell carcinoma of the thyroid or by amyloid solid carcinomas.

INDICATIONS AND USAGE

Therapeutic doses of Sodium Iodide I 131 Solution USP prepared with HICON™ are indicated for the treatment of hyperthyroidism and selected cases of carcinoma of the thyroid.

CONTRAINDICATIONS

Patients with vomiting and diarrhea should not receive radioiodide and concurrent antithyroid therapy should be discontinued 3-4 days before administration of radioiodide.

Sodium Iodide I-131 is contraindicated in women who are, or who may become pregnant. (**See Pregnancy section and Nursing section**).

WARNINGS

Sodium Iodide I-131 is not usually used for the treatment of hyperthyroidism in patients under 30 years of age unless circumstances preclude other methods of treatment.

PRECAUTIONS

General

The recent intake of stable iodine in any form, or the use of thyroid or anti-thyroid drugs will affect the uptake of radioiodide. Accordingly, the patient should be questioned carefully regarding previous medication and procedures involving radiographic contrast media.

Metabolic interactions:

- Hyperthyroidism and thyrotoxic cardiac disease may be aggravated by radiation thyroiditis. Pre–treatment and post-treatment with antithyroid agents and/or beta-blockers, such as propranolol should be considered.

- Low serum chlorides or nephrosis may increase thyroid uptake of Sodium Iodide I-131.

- Renal function impairment may decrease excretion of radioiodide and increase the amount of radiation exposure.

Radiopharmaceuticals should be used only by nuclear physicians and/or radiopharmacists who are qualified by training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized

to license the use of radionuclides (**See DRUG HANDLING AND FINAL DOSAGE FORM PREPARATION sections**).

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

Carcinogenesis

Experiments in animals with Sodium Iodide I-131 have demonstrated that radioiodide administration can induce thyroid adenomas and carcinomas. However, studies in humans have shown no conclusive evidence of thyroid carcinoma in hyperthyroid patients treated with Sodium Iodide I-131.

Mutagenesis

Mutagenic effects have not been clearly established in clinical studies of patients treated with Sodium Iodide I-131. However, chromosomal changes have been reported in laboratory studies.

Impairment of Fertility

A follow-up study of 627 women treated for differentiated thyroid carcinoma with Sodium Iodide I-131 revealed no evidence of fertility impairment.

Pregnancy Category X

See CONTRAINDICATIONS section.

Sodium Iodide I-131 may cause fetal harm to the thyroid gland when administered to a pregnant woman.

Radioiodide crosses the placenta and may cause severe and irreversible hypothyroidism in the neonate; the fetal thyroid begins to concentrate iodine during approximately the 12^{th} week of gestation.

The possibility of pregnancy should be assessed in women of childbearing potential. To avoid the possibility of fetal exposure to radiation, in those circumstances where the patient's pregnancy status is uncertain, a pregnancy test should be performed. Radioiodide therapy for the treatment of thyroid disease in women of childbearing age should only be performed when appropriate contraceptive measures have been taken or when pregnancy testing is negative.

Adequate and well controlled studies have not been performed in animals.

Nursing Mothers

Sodium Iodide I-131 is distributed into breast milk and may reach concentrations equal to or greater than concentrations in maternal plasma. Formula feeding should be substituted for breast feeding until radiation levels have substantially decreased.

Pediatric Use

Safety and efficacy in pediatric patients have not been established. (**See WARNINGS section)**.

Geriatric Use

Adequate and well controlled studies on the relationship of age to the effect of radioiodide have not been performed in geriatric population.

This drug is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

ADVERSE REACTIONS

Adverse events associated with the class of Sodium Iodide I-131 drug product include hypersensitivity reactions, radiation toxicities, and metabolic events.

Immediate adverse reactions typically are related to hypersensitivity; e.g., anaphylaxis, rash, hives, bronchospasm, and other allergic events.

Radiation adverse events are related to the dose include the following:

Bone marrow depression, leukopenia, thrombocytopenia, acute leukemia, anemia, blood dyscrasia, chromosomal abnormalities, radiation sickness, and death. Delayed radiation toxicity includes radiation thyroiditis, gastritis and sialadentis.

Metabolic adverse events include hypothyroidism and exaggerated hyperthyroidism due to radiation thyroiditis.

Tenderness and swelling of the neck, pain on swallowing, sore throat and cough may occur about the 3rd day after treatment.

INFORMATION FOR PATIENTS

Patients should inform their health care practitioner if they have one or more of the following:

- Inform your physician if you are pregnant. (**See PRECAUTIONS – Pregnancy**)
- Inform your physician if you are allergic to any drugs or food, or if you have immune, autoimmune, or immune deficiency disorders. Also, inform your physician if you had any reactions to previous injections of dyes used for x-ray procedures. (**see PRECAUTIONS – General**)
- Inform your physician of all medications you are currently taking, including non-prescription drugs (over-the-counter), before you have this procedure.

Patients should be advised to follow radiation safety precautions after receiving Sodium Iodide I-131 treatment to minimize the radiation contamination of other persons or the environment:

- Patients who receive Sodium Iodide I-131 should be advised that for several hours following administration, radioactivity will be present in excreted urine. To help protect themselves and others in their environment, precautions need to be taken for 12 hours following administration.
- Whenever possible, a toilet should be used rather than a urinal, and the toilet should be flushed several times after each use. Spilled urine should be cleaned up completely and patients should wash their hands thoroughly.
- If blood or urine gets into clothing, the clothing should be washed separately, or stored for 1-2 weeks to allow for decay of the I-131.
- Increase intake of fluids to promote more frequent voiding to help eliminate radioactive iodide.
- Avoid close or prolonged contact with others, especially children and pregnant women; sleep alone; avoid intimate contact.
- Wash sink and tub after use; use separate towels and washcloths; launder clothes and linen separately. Avoid handling another person's eating or drinking utensils, toothbrushes, and personal hygiene materials.

DRUG ABUSE AND DEPENDENCE

Patients administered Sodium Iodide I 131 Solution USP are not at risk for developing chemical dependency.

OVERDOSAGE

In the treatment of hyperthyroidism, over-dosage may result in hypothyroidism, the onset of which may be delayed. Appropriate replacement therapy is recommended if hypothyroidism occurs. Radiation absorbed doses to various tissues for any administered dose may be calculated by reference to Table 4 (Absorbed Radiation Doses I-131). (**See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS sections**).

DOSAGE AND ADMINISTRATION

The concentrated Sodium Iodide I 131 Solution USP provided with HICON™ must not be used for direct administration to patients. It must be diluted and prepared as described in the **DRUG HANDLING AND DOSAGE FORM PREPARATION** section.

The recommended dosage for orally administered Sodium Iodide I 131 Solution USP is based on the thyroid gland uptake as well as the size of the gland. Thyroidal uptake and size should be determined by the physician prior to treatment and may be useful in calculating the therapeutic dose to be administered to the individual patient. Recommended dosages of orally administered Sodium Iodide I-131 are:

Disease Therapy:

Antihyperthyroid Therapy:
Oral dose of 148 to 370 megabecquerels (4 to 10 millicuries).
Toxic nodular goiters and other serious thyroid conditions may require larger dosages.

Antineoplastic - Ablation of normal thyroid tissue:
Initial oral dose of 1.1 to 3.7 gigabecquerels (30 to 100 millicuries).

Subsequent ablation of metastases with oral dose of 3.7 to 7.4 gigabecquerels (100 to 200 millicuries).

General Dosing Information

Patients should be adequately hydrated before and after administration of radioiodide to assure rapid urinary elimination of the iodide that is not absorbed by the thyroid gland.

Radiation Dosimetry

Following administration of Sodium Iodide I-131, about 40 percent of the activity has an effective half-life of 0.34 days and 60 percent has an effective half-life of 7.61 days. On this basis, the estimated absorbed radiation dose to an average adult (70 kg) from an oral dose of 370 MBq (10 mCi) of Sodium Iodide I-131 is shown in Table 4.

Table 4
Absorbed Radiation Doses I-131

Tissue	mGy/370 MBq	Rads/10 mCi
Thyroid	350,000	35,000
Testes	92	9.2
Ovaries	93	9.3
Whole body	160	16.0

Method of Calculation: A Schema for Absorbed-Dose Calculations for Biologically Distributed Radionuclides, MIRD Pamphlet No. 1, J Nucl Med Suppl, 1:7, 1968.

DRUG HANDLING AND FINAL DOSAGE FORM PREPARATION

Drug Handling

1. The concentrated Sodium Iodide I 131 Solution USP provided with HICON™ should not be used after the expiration date stated on the container label.

2. The solution should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. The solution should not be used if cloudy, discolored, or found to contain particulate matter. However, it is well known that glass tends to darken in the presence of high radioactivity.

3. Care should be taken to minimize radiation exposure to the patient consistent with proper patient management and to insure minimum radiation exposure to occupational workers. Waterproof gloves should be used during the entire handling and administration procedure. Adequate shielding should be maintained during the life of the product.

Preparation of Dilute Sodium Iodide I 131 Solution USP

1. Using the calibration date and radionuclidic concentration on the label of the product vial, calculate the required volume to produce the necessary dose in MBq or mCi.

2. Using a shielded syringe, remove the required volume.

3. Using the shielded syringe, transfer the required volume to a suitably shielded receiving vial.

4. Add diluent solution to the receiving vial to produce a final dose of the desired volume. The recommended diluent is Purified Water USP containing 0.2% Sodium Thiosulfate USP as a reducing agent. The use of acidic diluents may cause the pH to drop below 7.5 and stimulate the volatilization of Iodine I-131 hydriodic acid.

5. The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

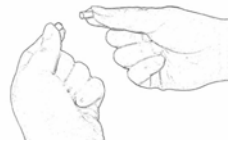
6. The finished preparation should not be used after the expiration date stated on the container label.

Preparation of Sodium Iodide I 131 Capsules USP

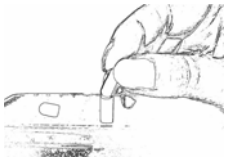
1. The kit includes one large gelatin capsule and one small gelatin capsule for each dose prepared. Each large capsule is empty and each small capsule contains approximately 300 mg of Dibasic Sodium Phosphate Anhydrous USP as the absorbing buffer.

2. Using the calibration date and radionuclidic concentration on the label of the product vial, calculate the required volume to produce the necessary dose in MBq or mCi.

3. Open one **LARGE** capsule by pulling apart the capsule into two pieces as illustrated below:



4. Insert an unopened **SMALL** capsule into the bottom half of the empty large capsule as illustrated below:



5. With an appropriate syringe, withdraw the required volume of Sodium Iodide I 131 Solution USP (maximum 150 μL) from the vial as illustrated below:

6. Inject into the center of the **SMALL** capsule through the top as illustrated below:

7. Slip the upper half of the large capsule over the bottom half to completely cover the small capsule and push down gently until locked as illustrated below:

8. After dispensing, the patient dose should be measured in a suitable radioactivity calibration system immediately prior to administration.

9. Store the capsule in a suitable polypropylene container and place inside a lead pot until use. The capsule should be used within seven days.

HOW SUPPLIED

Each HICON™ kit of 9.25 GBq (250 mCi) includes:
a) a blister package of ten small hard gelatin capsules each containing approximately 300 mg of Dibasic Sodium Phosphate Anhydrous USP as absorbing buffer.
b) a blister package of ten empty large hard gelatin capsules.
c) a 1 mL vial containing 0.25 mL of Sodium Iodide I 131 Solution USP, therapeutic oral solution containing approximately 9.25 GBq (250 mCi) at time of calibration.

Each HICON™ kit of 18.5 GBq (500 mCi) includes:
a) two blister packages of ten small hard gelatin capsules each containing approximately 300 mg of Dibasic Sodium Phosphate Anhydrous USP as absorbing buffer.
b) two blister packages of ten empty large hard gelatin capsules.
c) a 1 mL vial containing 0.5 mL of Sodium Iodide I 131 Solution USP, therapeutic oral solution containing approximately 18.5 GBq (500 mCi) at time of calibration.

Each HICON™ kit of 37 GBq (1,000 mCi) includes:
a) four blister packages of ten small hard gelatin capsules each containing approximately 300 mg of Dibasic Sodium Phosphate Anhydrous USP as absorbing buffer.
b) four blister packages of ten empty large hard gelatin capsules.
c) a 1 mL vial containing 1 mL of Sodium Iodide I 131 Solution USP, therapeutic oral solution containing approximately 37 GBq (1,000 mCi) at time of calibration.

Each mL of the aqueous product that comes with HICON™ contains:
37 gigabecquerels of Sodium Iodide I-131
< 2.0 mg of Disodium Edetate Dihydrate USP
< 4.4 mg of Sodium Thiosulphate Pentahydrate USP
< 40 mg of Dibasic Sodium Phosphate Anhydrous USP

Complete assay data are available on the container.

STORAGE

The Sodium Iodide I 131 Solution USP provided with HICON™ should be stored between 2°C and 25°C (36°F and 77°F).

NDC 65174-880-25 (for 250 mCi vial size)
NDC 65174-880-50 (for 500 mCi vial size)
NDC 65174-880-00 (for 1,000 mCi vial size)

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