Taiwan Food and Drug Administration

Assessment Report

Trade Name：INER Sodium Fluoride [F-18] Injection

Active Ingredient：Sodium Fluoride [F-18]

License Number：衛署藥製字第 R00032 號

Applicant：行政院原子能委員會核能研究所核醫製藥中心

Approval Date：2010/12/23

Indication：used as a bone imaging agent to defined areas of altered osteogenic activity

1. Background Information

Trade Name	INER Sodium Fluoride [F-18] Injection
Active Ingredient(s)	Sodium Fluoride [F-18]
Applicant	行政院原子能委員會核能研究所核醫製藥中心
Dosage Form & Strengths	Injection, each mLcontains more than 111 MBq (3 mCi) of sodium fluoride [F-18]
Indication	used as a bone imaging agent to defined areas of altered osteogenic activity
Posology	The recommended dose for adults is 185-370 MBq (5-10 mCi) as an intravenous injection. PET scanning is recommended to perform 0.5 to 2 hours after administration of sodium fluoride [F-18].
Pharmacological Category ATC Code	

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, sodium fluoride F 18 (^{18}F-NaF), has the molecular formula of Na^{18}F with a molecular weight of 40.99. It has radioactive nature and decays by positron emission. Due to the short half-life of radioactive nature, the drug substance is not isolated during the manufacturing process. Therefore, the specification is not proposed for the radioactive drug substance.

2.1.2 Drug product

INER [F-18] Sodium Fluoride Injection is provided as a ready-to-use sterile, pyrogen-free, clear and colorless solution. Each vial contains more than 111 MBq/ml of sodium fluoride F 18 (^{18}F-NaF) in isotonic sodium chloride injection.

The product is prepared through sterile filtration, aseptic filling and package after the synthesis is completed. The critical steps are identified. The process validation is performed on three consecutive maximum- and minimum-sized batches. The results are complied with the predetermined acceptance criteria. The products are released according to the analytical methods and acceptance criteria. The testing comprises the appearance, identification, pH, radiochemical purity, radionuclidic purity, chemical purity, sterility and endotoxin. Non-pharmacopoeia methods are validated in terms of specificity, linearity, accuracy, precision, quantitation limit/detection limit and

robustness. The acceptance criteria are consistent with European Pharmacopoeia.

Stability tests are performed for three batches under room temperature (15-30°C) and evaluated with the appearance, pH and radiochemical purity. The data are available up to 8 hours, which support a shelf-life of 8 hours in room temperature. Information on the finished product have been presented and regarded as appropriated.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

INER Sodium Fluoride [F-18] Injection, a positron-emitting radiopharmaceutical containing no carrier-added (NCA) radioactive fluoride 18F, is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging The estimated absorbed radiation doses to a human adult (70 kg) from intravenous administration of Sodium Fluoride [F-18] Injection are provided. Bone and bone marrow are considered the target and critical organs. To minimize the radiation-absorbed dose to the bladder, adequate hydration should be encouraged to stimulate frequent voiding during the first few hours after intravenous administration.

2.2.2 Toxicological Studies

Studies with Sodium Fluoride [F-18] Injection have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility. Animal reproduction studies have not been conducted with Sodium Fluoride [F-18] Injection. In contrast, the toxicology of the non-radioactive sodium fluoride is well established due to extensive use in municipal water fluoridation systems, various dental products, and in a variety of industrial applications. The in vitro data indicate that the genotoxicity of fluoride is limited primarily to doses much higher than those to which humans are exposed on a daily basis. In addition, genotoxic effects are not always observed, even at high doses, and the preponderance of the genotoxic effects that have been reported are of the types that probably are of no or negligible genetic significance.

The toxicology of Sodium Fluoride [F-18] Injection will be the same as that of the non-radioactive compound, except for the radiation exposure. However, the amount of fluoride ions in Sodium Fluoride [F-18] Injection at the indicated dose is very low, and provides assurance that toxic effects will not be observed.

In conclusion, fluoride is a normal body constituent. The maximum amount of fluoride ions in Sodium Fluoride [F-18] Injection (<1.3 mg/70 kg) at the indicated dose is expected to have minimal effect on normal human physiology. Sodium Fluoride [F-18] Injection is a radiopharmaceutical, and should be handled in accordance with

all applicable regulations.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following intravenous administration, fluoride ^{18}F ions equilibrate rapidly, primarily with the extracellular fluid space. It accumulated in the skeleton, with greater deposition in the axial skeleton than in appendicular skeleton, and greater deposition in the bones around joints than in the shafts of long bones. Increasing deposition has been investigated in bone around fracture sites. The protein binding rate is low. The rapid plasma clearance was observed. Urine excretion is the major route of elimination. The fluoride ^{18}F ions are rapidly cleared by bone deposition and more than 20% excreted into the urine in the first 2 hours following intravenous administration. Subsequently, the small residues of fluoride ion continue to be excreted in urine and further resulting diminishing radioactivity of fluoride ions in soft tissues of body. The potential of milk secretion of fluoride ^{18}F was unknown and caution should be exercised when it is administered to a nursing mother.

2.3.2 Interaction Studies

Based on the pharmacokinetic characteristics of sodium fluoride and its clinical practice, the drug-drug interaction of INER Sodium Fluoride [F-18] Injection could be waived.

2.3.3 Special Populations

Based on the pharmacokinetic characteristics of sodium fluoride and its clinical practice, lack of PK information in special populations is acceptable.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Four key journal articles were provided to support the accuracy of INER Sodium Fluoride [F-18] Injection (9 mg/ml) as ” a bone imaging agent to define area of altered osteogenic activity”.

Study 1 was to compare $Na^{18}F$-PET and routine BS (bone scintigraphy) in terms of accuracy of diagnosis of osseous metastases in patients with breast cancer and suspected metastatic bone involvement. $Na^{18}F$-PET and BS were compared using ROC curve analysis (Hanley and McNeil, 1983) with sample unit of patient-by-patient and lesion-by-lesion. Study 2 was to evaluate the accuracy of planar RNB (radionuclide bone scanning) versus tomographic bone imaging with ^{18}F-labeled NaF and PET ($Na^{18}F$-PET) in detecting osteolytic and osteoblastic metastases and its dependency on their anatomic localization. RNB and $Na^{18}F$-PET were compared

using lesion-by-lesion analysis using ROC curve analysis. In Study 3, lung cancer patients were prospectively examined with planar BS, SPECT of the vertebral column and PET using F-18 sodium fluoride ($Na^{18}F$-PET) for detection of bone metastases. $Na^{18}F$-PET and BS with and without SPECT were compared on a patient basis using ROC curve analysis; Study 4 was to evaluate the clinical value of planar bone scans, SPECT and ^{18}F-labeled NaF PET ($Na^{18}F$-PET) imaging on the management of patients with newly diagnosed lung cancer. BS with and without SPECT and $Na^{18}F$-PET were compared on a patient basis using ROC curve analysis.

For the ROC curve, all lesions and all disease were rated using a five-point scale (1: definitely metastatic, 2: probably metastatic, 3: equivocal, 4: probably not metastatic, 5: definitely not metastatic). The comparisons of area under the ROC curves for each study were listed in Table 1.

Table 1 Comparison of the area under the ROC curves for each study

Study	Basis	F-18-PET	BS/RNB	BS+SPECT	p-value (F-18-PET vs. other method)
1	Patients	1	0.82	-	<0.05
	Lesions	0.99	0.72	-	<0.05
2	Lesions	0.99	0.64	-	<0.05
3	Patients	0.989	0.771	0.875	Both <0.005
4	Patients	0.993	0.779	0.944	vs. BS: <0.05 vs. BS+SPECT: >0.05

In these four key journal articles, some design defects might cause a bias in evaluating the accuracy of $Na^{18}F$-PET in the detection of bone metastases. However, the results of four studies consistently demonstrated that the accuracy of $Na^{18}F$-PET in detecting bone metastases was very close to the accuracy of the reference methods (area under the ROC curve very close to 1), and was significantly higher than the accuracy of planar bone scan using the ROC curve analysis ($p<0.05$). Therefore, the efficacy was acceptable.

2.4.2 Safety Results

There was no adverse reaction noted in over 400 patient studies reported in the medical literature. The safety was not evaluated for subjects aged $\leqq$18 years old.

2.5 Bridging Study Evaluation

The majority of submitted articles were Caucasian data. However, considering the pharmacokinetic characteristics of $Na^{18}F$ and the indication, the potential of ethnic sensitivity would be minimal. In addition, the clinical experience of $Na^{18}F$ in Taiwan was provided. Therefore, the bridging study was waived.

2.6 Conclusion

The document of CMC, pharmacology/toxicology, pharmacokinetics, statistical and clinical sections could support the efficacy and safety. The approved indication is “bone imaging agent to define area of altered osteogenic activity”. The adult dosage is 4-10mCi given intravenously, and the image should be performed 30min to 2hours after $Na^{18}F$ administration.

3. Post-Marketing Requirements

Routine post-marketing surveillance as required by Department of Health