N1177

Summary History and Technical Description*

I. Historical Background

N1177 has an impressive pedigree and rich investment history. N1177 was originally developed by pharmaceutical giant Sterling Winthrop as a next generation, proprietary product to expand the company's existing portfolio of diagnostic imaging drug products. Sterling Winthrop was purchased by Eastman Kodak and the N1177 asset was held in Kodak's NanoSystems division and later licensed to the diagnostic imaging division of Hafslund Nycomed AS. Over $50 million was invested in N1177 between Kodak/Sterling Winthrop and Nycomed, which encompassed comprehensive pharmaceutical development, extensive preclinical investigations, an Investigational New Drug (IND) application, and Phase I and early Phase II clinical trials for use as a lymphography agent. Nycomed discontinued work on N1177 because the lymphography market in the late 1990s was relatively small and Nycomed was already invested in three ultrasound contrast agents which were also under development. Nycomed (its Amersham division was later purchased by GE) contracted with Massachusetts General Hospital (MGH) as its agent to license the technology to Photogen, which later became Imcor, which was dissolved in 2005 and sold to NanoScan Imaging.

II. Technical Description

Active Pharmaceutical Ingredient: 6-Ethoxy-6-oxohexyl-3,5-bis(acetylamino)-2,4,6-triiodobenzoate.

Molecular Formula: C19H23N2O6I3; Molecular Weight: 756.12; Formulation: Milky white, ready-to-use suspension. Physicochemical characteristics: Description White to off-white solid

The drug substance is prepared by the reaction of sodium diatrizoate with ethyl 6-bromohexanoate in dimethylformamide. Purification is achieved by precipitation from dimethyl sulfoxide and water, followed by slurrying the drug substance in hot ethanol. It is practically insoluble in water; pKa was not observed over the pH range of 1.8 to 12.2 [compound is water insoluble; methanol used as a cosolvent; results obtained by extrapolation to zero percent solvent].

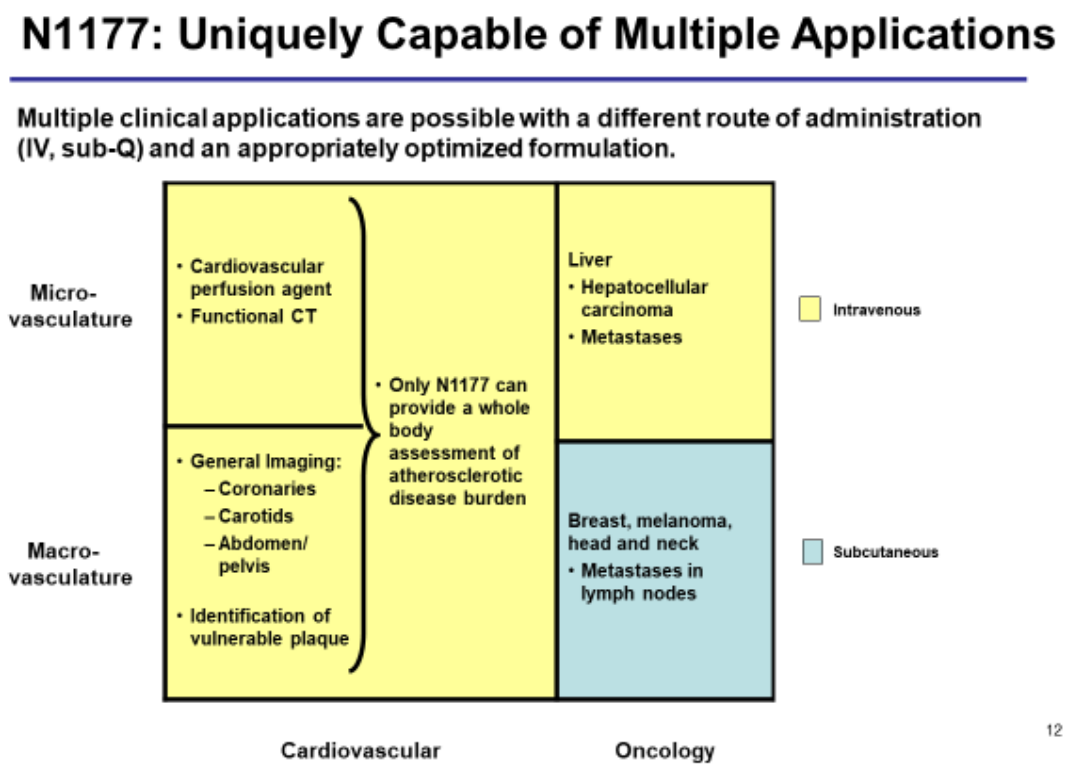
N1177 INJECTABLE SUSPENSION, 150 MG/ML is a terminally heat-sterilized nanoparticulate formulation (median particle size not more than 350 nm) of the x-ray contrast agent N1177 [formerly referred to as WIN 67722] (15% (w/v)) stabilized by the excipient diafiltered Poloxamer 338 [formerly referred to as WIN 22288, 3% (w/v)], with the inclusion of PEG-1450 [polyethylene glycol 1450, 15% (w/v)), and buffered with tromethamine. N1177 is prepared from commercially available sodium diatrizoate in a one-step synthesis. It contains two ester moieties, one of which can be hydrolyzed enzymatically to give a water-soluble analog, WIN

68056, thus enhancing clearance from the body. N1177 was originally developed by Sterling Winthrop as a replacement for water-soluble iodinated contrast media (CM).

N1177 is an iodinated nanoparticulate formulated as an emulsion (see above). The excipient Poloxamer not only stabilizes the formulation, it also "stealths" the particles following initial injection so that they are not immediately recognized by activated macrophages. Following subcutaneous/intravenous injection the excipient washes off and the exposed nanoparticles are taken up by activated macrophages and become sequestered in tissues rich in macrophages, e.g., the spleen and the liver. The particles also become sequestered in areas of vascular inflammation where activated macrophages play an important role.

III. Disruptive Platform Technology

N1177 promises multiple, significant "platform" opportunities: (a) General x-ray/CT imaging agent replacing most water-soluble iodine contrast agents; (b) Blood pool agent with an extended residence time allows up to 30 minutes to image multiple vascular beds with a single injection (e.g., carotid arteries, coronary arteries and peripheral arteries); (c) Mapping of metastatic deposits within lymph nodes; (d) Organ perfusion, includes detection of liver and other cancers; (e) Identification of vascular inflammation / atherosclerotic plaques /vulnerable plaques; (f) CNS and autoimmune diseases where inflammation plays a central role.



PRECLINICAL IMAGING STUDIES: ONCOLOGY (SUBCUTANEOUS ROUTE OF ADMINISTRATION)

Studies in miniature swine bearing cutaneous melanomas demonstrated the efficacy of N1177 INJECTABLE SUSPENSION, 150 MG/ML in a tumor model with characteristics similar to the human disease. After subcutaneous perilesional administration of N1177 INJECTABLE SUSPENSION, 150 MG/ML, draining lymph nodes containing metastases had filling defects on CT scans, which were confirmed histologically. Normal lymph nodes were uniformly opacified.

Studies in normal dogs demonstrated dose-dependent opacification of axillary and supraclavicular nodes or the popliteal, inguinal, and paraaortic nodes following subcutaneous injection of N1177 INJECTABLE SUSPENSION, 150 MG/ML in the forelegs or hind legs, respectively. Likewise, imaging has been shown in neck and mediastinal nodes, following injection in the tracheal submucosa; rectal nodes, following injection into the rectal submucosa; and primary echelon nodes and paraaortic nodes draining the prostate or cervix, following injection around these organs. Thus, administration of N1177 INJECTABLE SUSPENSION, 150 MG/ML is expected to opacify the nodal systems involved in the staging of head and neck, prostate, male and female pelvis, rectal, lung, skin (melanoma), and breast cancers.

PRECLINICAL IMAGING STUDIES: ONCOLOGY (INTRAVENOUS ROUTE OF ADMINISTRATION)

After intravenous administration of N1177 the nanoparticles are extracted from the blood by cells of the RES, Kupffer cells, and as a consequence localize in normal hepatic parenchyma. In CT images acquired after the administration of N1177, tumors will be visualized as relatively low attenuation, low density (dark) features within a background of high attenuation, high density (bright) normal parenchyma.

PRECLINICAL IMAGING STUDIES: CARDIOVASCULAR DISEASE (INTRAVENOUS ROUTE OF ADMINISTRATION)

N1177 was evaluated extensively both in vitro and in vivo for its ability to detect macrophages with CT. First, the uptake of N1177 by macrophages was tested in vitro. Subsequently, the in vivo kinetics and distribution of N1177 in the blood and in macrophage rich tissues were determined after intravenous injection in rabbits. Finally, N1177 was tested in a model of atherosclerotic plaques generated by balloon injury in the aorta of hypercholesterolemic rabbits. Atherosclerotic plaques in this animal model contain high levels of macrophage infiltration and are similar in size to human coronary atherosclerotic plaques. In this model, it was shown that an increase in density can be detected in atherosclerotic plaques of rabbits 2 h after intravenous injection of N1177 and that this increase was correlated with macrophage infiltration in corresponding histological sections. In conclusion, macrophage infiltration can be detected in atherosclerotic plaques with a clinical CT scanner after intravenous injection of the nanoparticulate contrast agent N1177.

ADME STUDIES

The absorption, distribution, and excretion of N1177 has been studied in rats and dogs given single subcutaneous doses of N1177 INJECTABLE SUSPENSION, 150 MG/ML or intravenous doses of solubilized N1177. After subcutaneous administration, the radioactivity was eliminated from the plasma with a terminal half-life of 5 and 11 days in rats and dogs, respectively. The

excretion of radioactivity after intravenous administration was more rapid, with approximately 70% being eliminated from the plasma in the first 24 and 48 hours in rats and dogs, respectively. In rats, the major route of elimination was the feces (~60%). N1177 was excreted in both species primarily as the carboxylic acid metabolite, WIN 68056. Tissue retention studies (6 month duration) in dogs after subcutaneous administration of N1177 INJECTABLE SUSPENSION, 150 MG/ML have shown that, although the concentration of radioactivity achieved in draining lymph nodes is significantly greater than the corresponding systemic concentrations, the elimination rates are similar. N1177 was the singular component observed in profiles of axillary node and injection site homogenates.

IV. CLINICAL IMPACT

N1177 is water insoluble, giving it multiple advantages over other contrast media ("CM") including:

- improved safety due to unique pharmacokinetics,
- less invasive,
- less radiation,
- improved image quality, and
- extended imaging time.

Because N1177 is formulated as a nanoparticle suspension and is therefore taken up by macrophages, it is possible to control its biodistribution in a manner that presents opportunities for imaging the functionality of anatomical structures that are not possible with traditional CM, while providing a high assurance of patient safety. N1177 is unique in that it is primarily cleared through the liver unlike traditional CM that are primarily cleared through the kidneys, which can result in renal toxicity.

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