What is NeutroSpec?

NeutroSpecTM or Technetium (99^{m} Tc) fanolesomab is a radio-labeled monoclonal antibody. Fanolesomab, the monoclonal antibody component, binds CD15, a protein found primarily on the surface of white blood cells. The radioactive component is Technetium-99m.

What is NeutroSpec used for?

NeutroSpec is approved to aid in the diagnosis of appendicitis in patients with equivocal signs and symptoms of appendicitis who are 5 years of age and older.

What is Equivocal Appendicitis?

Appendicitis is an infection of the appendix, a part of the large intestine; patients with appendicitis often have fever, an elevated white blood cell count, and pain in the right lower portion of the abdomen. If not treated by removal of the appendix (appendectomy), it can lead to a ruptured appendix and a more serious infection called peritonitis. Equivocal appendicitis refers to cases in which one or more of these conventional signs of appendicitis are missing, leading to doubt about the diagnosis and uncertainty about whether the patient should undergo surgery. It is important to know whether a patient has a condition such as appendicitis that can be treated successfully by an operation before subjecting the patient to the risks of surgery.

How is NeutroSpec given and used?

The antibody must first be combined with technetium-99m, usually in the nuclear medicine department, to prepare NeutroSpec. Because the radioactivity decays with time, NeutroSpec must be used within a specific time period. It is given to the patient, usually in the nuclear medicine department, by intravenous injection. The antibody will bind to white blood cells in the body and the technetium will give off detectable radiation showing the location of white blood cells in the body. If the patient has appendicitis, white blood cells will be concentrated in the appendix, helping the surgeon in making the diagnosis of appendicitis. If white blood cells are not concentrated in the appendix, it is less likely that appendicitis is present. NeutroSpec does not treat appendicitis itself. In clinical trials, NeutroSpec was not always accurate; however, in the clinical studies, it correctly identified the presence or absence of appendicitis in approximately 90% of patients without classic signs and symptoms of appendicitis.

Why is marketing of NeutroSpec being suspended?

In the post-marketing period, 17 patients who received NeutroSpec developed life-threatening side effects soon after it was injected. The major side effects included shortness of breath, low blood pressure, and cardiac and pulmonary arrest. Patients needed treatment with fluids, medications to increase their blood pressure, and oxygen. In two cases, the affected patients died. Because of the possibility that NeutroSpec was

related to these life-threatening events and other methods to diagnose appendicitis are available that do not have the risk of these events occurring, Palatin Technologies, the manufacturer of NeutroSpec, has voluntarily suspended marketing of this product. All of the reactions occurred immediately after NeutroSpec was administered. There is no evidence that patients who already safely received the drug face any long-term risk.

What other steps has the manufacturer taken?

The manufacturer is notifying physicians of these cases and informing them that use of NeutroSpec should be discontinued until further notice. The manufacturer will closely evaluate the possible ways in which NeutroSpec may be causally associated with the adverse reactions. Health care providers have been informed that any potential adverse events that have occurred in a patient receiving NeutroSpec should be reported to Palatin, or to the FDA's MedWatch reporting system by telephone (1-800-FDA-1088), facsimile (1-800-FDA-0178), the MedWatch Web site at www.fda.gov/medwatch, or mailed to MedWatch (HF-2, 5600 Fishers Lane, Rockville, MD 20853-9787). The FDA will maintain close contact with the manufacturer during this process and issue further information as it becomes available.

Did the patients who developed these side-effects have other possible reasons to develop these reactions?

A majority of patients who developed these side-effects had serious medical conditions such as diabetes that may have predisposed them to these reactions. However, some patients experiencing these reactions did not have a serious pre-existing condition.

What kinds and numbers of patients have received NeutroSpec?

Before it was approved for marketing, NeutroSpec was evaluated in clinical trials that included about 500 people; about half had suspected appendicitis but were equivocal with regard to their signs and symptoms; other people who received NeutroSpec included healthy volunteers or patients with other types of infections. According to Palatin, approximately 11,000 patients have received NeutroSpec since its approval; however, the majority of these patients received NeutroSpec to aid in the diagnosis of infections other than appendicitis.

Does NeutroSpec work for the diagnosis of infections other than appendicitis?

Definitive safety and efficacy data are only available for appendicitis. Clinical studies are necessary to determine if NeutroSpec aids in the diagnosis of infections other than appendicitis.

Why couldn't the FDA just restrict use of NeutroSpec to its approved indication?

Some patients who received NeutroSpec for its approved indication (the diagnosis of appendicitis in patients with equivocal signs and symptoms) developed reactions of a

similar nature, although they did not rise to the level of life threatening. Since any patient who receives NeutroSpec is potentially at risk for developing a life threatening reaction, restricting use to the approved patient population will not eliminate the risk. Based on this information, the risks of NeutroSpec appear to outweigh its benefits, even when used as approved.

Are there any other methods available to diagnose equivocal appendicitis?

The standard methods, physical examination, standard lab tests such as measurement of the white blood cell count, an indicator of the possible presence of infection; and imaging methods such as ultrasound or computerized tomography (CT) are capable of diagnosing most cases of appendicitis. In unusual cases in which the diagnosis remains in doubt, use of a technique called laparoscopy, which involves insertion of a fiber-optic scope inside the abdomen, can be used to determine whether appendicitis is present; this same method can be used to treat appendicitis.

Is NeutroSpec better at diagnosing appendicitis than these other methods?

The are no definitive studies that directly compare NeutroSpec to these other methods to determine if NeutroSpec is better at diagnosing appendicitis than the other methods. In the clinical trials, some patients had one or more of these other modalities before they received NeutroSpec .

Do these other methods have life-threatening risks?

Physical examination, blood tests, and ultrasound examinations have very little risk. Contrast agents used for CT scans can produce allergic reactions, but these are rare; in addition, a form of CT scanning called helical CT that does not use contrast agents can be used in the diagnosis of appendicitis. Laparoscopy can rarely result in serious complications. With all of these methods, the frequency of life-threatening adverse events is much lower than for those observed with use of NeutroSpec.

What if physicians need NeutroSpec to diagnose a patient with equivocal appendicitis?

The FDA is working with the manufacturer to make NeutroSpec available on an investigational basis for cases in which the diagnosis of appendicitis cannot be confirmed or excluded by other methods. It should be emphasized that such situations are unusual; however, the FDA is committed to ensuring appropriate availability in such cases.

When was NeutroSpec approved?

NeutroSpec received approval in June 2004.

Why was NeutroSpec approved?

The company submitted data from adequate and well-controlled trials to the FDA showing that NeutroSpec was safe and effective as an aid to the diagnosis of appendicitis in patients with equivocal (non-classic) signs and symptoms.

Shouldn't the FDA have known this might happen?

The serious nature of the events that led to the suspension of NeutroSpec marketing were not seen in the studies used to support approval of NeutroSpec. It is not uncommon for new and/or more severe adverse events to be discovered once a drug is given to a larger number of patients, including patients who might be sicker or have co-existing medical conditions, than in the original clinical trials that led to approval.

Was the withdrawal of NeutroSpec discussed with the Drug Safety Oversight Board?

The Board was told about the ongoing assessment of the observed adverse events associated with the use of NeutroSpec.

How long will this suspension last?

The availability of NeutroSpec in the future will depend on the analyses of the data being obtained by the drug's manufacturer. The FDA may require that new clinical trials be conducted to show that NeutroSpec is safe and effective before marketing resumes.

How long has the FDA known about this situation?

The two reports of death following NeutroSpec administration were initially reported as possibly related to myocardial infarctions and were reported to the FDA's Medwatch program in April and May, 2005, respectively. Periodic safety reports, submitted to the FDA in July and October, 2005 consisted of additional reports citing serious reactions also occurring within minutes of NeutroSpec injection. FDA staff has since been working with the company to obtain more information about the postmarketing safety profile in order to determine the best course of action for the public health .

What is the FDA doing about this situation?

In addition to issuing this advisory, FDA has been in close contact with the manufacturer of NeutroSpec, and concurs with their decision to voluntarily suspend marketing of NeutroSpec and dosing of NeutroSpec in clinical trials. FDA is working with the manufacturer to develop studies, such as laboratory and animal studies that may help explain the major safety risks to humans. Additionally, FDA and the manufacturer are discussing options for safe clinical investigation of the product in situations where the potential benefit of the product is substantial.

What are other adverse reactions have been reported with NeutroSpec?

The most frequent adverse events, reported in about 2% of patients in clinical trials of NeutroSpec, were transient flushing and shortness of breath.

I've received NeutroSpec. Am I going to develop these symptoms?

In all the cases reported to the FDA, the serious adverse events occurred within, at most, an hour after injection of NeutroSpec, and generally within 5 minutes. If symptoms have not developed by then, they are extremely unlikely to occur.