

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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SUMMARY REVIEW



Food and Drug Administration

Center for Drug Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852**Memorandum**Division of Therapeutic Biological Internal Medicine Products
HFM-576

Date: June 30, 2004

From: M. Walton, MD, PhD, Director, DTBIMP/ODE6/CDER *M Walton*Subject: Supervisory Review Summary
BLA 103928 / 0
NeutroSpec: Fanolesomab radiolabeled imaging kit
Submitted by Palatin Technology

To: File STN 103928 / 0

Introduction

This BLA relates to the product NeutroSpec, a kit for the preparation of technetium (99m Tc) fanolesomab. Fanolesomab is a murine IgM monoclonal antibody which binds to the human CD15 antigen. This antigen is primarily found on polymorphonuclear neutrophils, eosinophils, and monocytes, but also occurs in many human tissues. Tc bound fanolesomab thus radiolabels human white blood cells and myeloid precursor cells; the majority of the circulating cell-bound radiolabel is found on PMNs.. This product is proposed

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This BLA was originally received by CBER in November 1999, assigned BLA # 99-1407 according to the administrative tracking system in use at that time. Initial reviews of the BLA were completed in 2000. A public Advisory Committee meeting of the Medical Imaging Device committee (MIDAC) was also held in July 2000 to discuss this BLA. In September 2000 a CR letter was issued to Palatin citing the CMC and facility related matters that were preventing approval of the product at that time. Palatin did not submit a complete response to the CR letter until October 2003. At that time, review of the BLA re-commenced.

A substantial number of review documents were written due to the prolonged history and difficult CMC issues of this product. These review documents are the basis from which this summary memorandum draws; and include the following:

CMC review of L. Epps, August 2000
CMC review of C. Fuchs, September 2000
Toxicology and Clinical Pharmacology Summary of M.D. Green
Clinical Review of R. Linblad, 2000

Clinical Imaging Review of L. Martynec, originally of 2000,
version with added clarifications, June 2004
CMC Resubmission reviews of C.Fuchs, L. Epps, D. Frucht, June 2004
Clinical Review of K. Ayalew, June 2004

Terminology of note includes that the early reviews refer to the product as "LeuTech". This was the trade name initially proposed by Palatin in 1999 for the fanolesomab imaging product. However, this name was determined to have unacceptable risk of medication errors by DMETS in 2004, and was not accepted by FDA for use, as described in the Trade Name section of this document. The trade name of NeutroSpec was subsequently selected and adopted. Therefore, at various places in the review documents this product may be referred to as LeuTech, fanolesomab, or NeutroSpec. Also as noted above, this BLA was initially tracked under a prior system, so the initial reviews refer only to the 99-1407 BLA number.

This document will summarize the major findings of the review of this BLA, and provide supervisory recommendation. However, only brief review of selected elements of the complete information is provided. The complete review documents, noted above, should be consulted directly for complete details of the review findings.

Chemistry

NeutroSpec is a kit for the preparation of the imaging agent. The kit contains fanolesomab and Cenolate (ascorbic acid for injection) as well as full instructions for use. Preparation of the imaging agent requires additional materials not contained in the kit; most notably sodium pertechnetate Tc-99m.

Palatin Technologies has ultimate control of all steps in the manufacturing of the product, is responsible for product release at each stage of manufacturing, and conducts QC release testing for NeutroSpec at their facility in NJ. Manufacturing is performed (b) (4) The fanolesomab antibody is manufactured at DSM in The Netherlands. DSM (b) (4) (b) (4) DSM, (b) (4) (b) (4) to Ben Venue Laboratories in Ohio for the (b) (4) filling, packaging and labeling.

Fanolesomab is a murine IgM antibody that is directed against the 3-fucosyl-N-acetyllactosamine moiety that defines the CD15 antigen. The RB5 cell line that produces fanolesomab was derived from an initial murine hybridoma which originated at the Wistar Institute. Because of the nature of the product's derivation, the exact amino acid sequence of the antibody is not known.

Major issues in the original submission that resulted in a CR letter included multiple CMC concerns and requests. These issues were responded to by Palatin, and have been substantially addressed. A notable insufficiency in the responses relate to Palatin's assay for antibodies against fanolesomab.

The HAMA assay is not presently validated. While this does not preclude approval of the product at this time, the CMC reviewers recommend that Palatin develop and validate an improved HAMA assay as a postmarketing commitment.

Comment:

This proposal is endorsed, and should be made a component of the approval of NeutroSpec.

Stability testing was validated for up to 24 months of storage.

Additional PMC requests related to CMC matters, as described in the full CMC review, include continued re-evaluation of drug specifications, development of carbohydrate specifications, improvements in the potency assay materials, shipping validation, additional stability testing and protocol development, and genetic stability testing.

Toxicology

Fanolesomab did not bind to circulating neutrophils of multiple tested laboratory animals, including 3 species of monkey. Thus, preclinical toxicology was expected to be uninformative. Conforming to this expectation, in two toxicology studies (1 each in rabbits and mice) given a single dose of fanolesomab, no effects were observed.

Clinical Pharmacology

No significant binding to RBCs in human blood samples. Binding was restricted to leukocytes. When approximately 10% of surface antigen did have bound antibody an in vitro assay of phagocytic activity showed approximately 20-30% decrease in activity. At 4% or less of saturation no changes were observed in cellular functions. Assuming uniform distribution of fanolesomab over the PMN population after injection, a 100 µg dose is expected to lead to approximately 0.4% saturation, well below the 4% no-impairment level.

In human studies, while a statistically significant transient decrease in WBC count occurred over the first hour following injection, followed by a increase at 4 hours post injection, the WBC count had returned to baseline approximately 18-24 hours post injection. The magnitude of these changes were generally small and not clinically meaningful. The physiological basis for this change is not known.

Tissue cross-reactivity was assessed and the antibody does bind to surfaces of a wide range of cells, including resident histiocytes or Kupffer cells, alveolar macrophages, glial cells, other brain cells (e.g. in cerebrum, cerebellum, spinal cord), perithelial cells, mucosal surface cells (e.g. in esophagus, stomach), glandular cells (e.g. pancreas, salivary gland) and mesothelial cells. Fanolesomab, as it is an IgM antibody is not expected to cross the blood brain barrier readily, so that CNS cells are not likely to be significantly exposed; no binding was observed to peripheral neuronal tissue. In addition, it is expected that tissue binding will be low as the circulating PMNs will be the most directly antigen-site exposed, and the circulating PMNs possess antigen sites far in

excess of the injected fanolesomab binding capacity. Thus that antibody entry tissue extracellular space (out of the vascular flow) and exposure to tissue specific cells is expected to be low.

Clinical Efficacy

Overview

Although the diagnosis of appendicitis is usually straightforward, there remain cases that are uncertain after consideration of history, physical exam, and routine clinical laboratory evaluations. Diagnostic imaging techniques are often employed in such cases, and can include CT scans and/or ultrasound. The clinical studies of this product evaluate another approach. Fanolesomab is a murine IgM antibody that binds predominantly to PMNs (although certain other cell types also exhibit binding). After radiolabeling of the antibody, it was hoped that nuclear medicine imaging would identify sites of acute inflammation; specifically the appendix in cases of true but clinically equivocal appendicitis.

Studies conducted by the sponsor to evaluate this use consist of a 10 patient phase 1 study, a 56 patient phase 2 study, and a 203 patient phase 3 study. At the time of the resubmission, an additional 83 patient experience was also submitted. In addition to the appendicitis studies, there were in 2000 also 140 patients with safety experience from studies in osteomyelitis or other infectious process studies.

Phase 3 Study

This was a multicenter, single arm, within patient comparison study of patients with equivocal signs, symptoms, and standard clinical laboratory findings of appendicitis. Three blinded readers were used to assess the images after the end of the study. These assessments were compared to the study site's final diagnosis, based upon all available information, including surgery and pathology reports when surgery was performed, and follow up at two weeks later when surgery was not performed. Eligibility criteria were clearly defined as to the qualifying nature of the atypical history, signs, or symptoms (these entry criteria had been refined after the analysis of the phase 2 study). Of note, patients with pelvic inflammatory disease were excluded from the study, thus imaging performance in patients with PID can not be determined.

The referring surgeon completed a questionnaire prior to the scan results that identified the estimated likelihood of appendicitis, and the planned management for the patient (discharge, continued in hospital observation, or prompt surgery). This questionnaire was also completed after the scan results were provided to the surgeon.

The 203 patients enrolled in this study were 60% female, and predominantly Caucasian (73%), with 16% Hispanic, 8% black patients. The age range was 5 to 85 years old. There were 10 sites, of which 5 sites enrolled 19-39 patients each, with 3 to 11 patients at the remaining 5 sites. Overall, the rate of appendicitis in the final diagnosis was 30%. At the 5 larger sites, the appendicitis rate

ranged from 11 to 36%. Only 2 of these patients were non-evaluable due to loss to follow-up, and only 1 due to failure to image sufficiently.

Planned parameters to characterize the scan performance included:

- Agreement or Accuracy: True Positive + True Negative / All Patients
- Sensitivity: True Positive / True Positive + False Negative
- Specificity True Negative / True Negative + False Positive
- Positive Predictive Value True Positive / True Positive + False Positive
- Negative Predictive Value True Negative / True Negative + False Negative

Where True positive / negative; False negative / positive indicates the scan’s categorization in light of the correct categorization as defined by the final clinical diagnosis.

The primary performance, based upon the aggregate of the 3 blinded readers, is shown below:

Phase 3 Study Primary Results - Blinded Independent Readers					
Accuracy	Totl Patients 200	True Positive + True Negative 175	Agreement Percentage 88	95% C.I. 82 92	
Sensitivity	Totl Positive Patients 59	True Positive 44	Sensitivity 75	95% C.I. 62 85	
Specificity	Totl Negative Patients 141	True Negative 131	Specificity 93	95% C.I. 87 97	
Positive Predictive Value	True Pos + False Pos 54	True Positive 44	PPV 82	95% C.I. 69 91	
Negative Predictive Value	True Neg + False Negative 146	True Negative 131	NPV 90	95% C.I. 84 94	

The on-site reader performance measures were similar for accuracy (88%), specificity (87%), and NPV (95%); but modestly different for sensitivity (90%) and PPV (74%).

The inter-reader concordance among the 3 possible pairings of readers ranged from 88% to 90%; the kappa statistics were 0.54 to 0.55.

Due to the nature of the entry criteria, a limited number of patients qualified as equivocal for the study, but were infact either very likely to have to appendicitis, or very unlikely to have

appendicitis. Focusing upon the 172 patients with the most equivocal status, of whom 29% did in fact have appendicitis, the sensitivity was 73%, specificity 93%, PPV 80%, and NPV 90%. Thus, the 28 patients who could have been diagnosed clinically without the scan with much better accuracy than the “very equivocal” patients did not bias the scan performance figures to any important degree.

Similarly, limiting analysis to just those patients who had a pre-scan planned management of in-hospital observation, the scan performance characteristics were largely the same as for the study overall.

Women in the reproductive age range (n=52) had similar performance characteristics.

Comparing the pre-scan planned management and the post scan planned management, 2 patients who would have been discharged both pre-scan and post-scan did have appendicitis, 2 patients would have been kept for observation rather than discharged, but did not have appendicitis, and 5 patients would have been shifted from discharge to prompt surgery, although this was inappropriate in 2 (but appropriate in 3). Of 39 patients shifted from observation to discharge, none was an inappropriate change; although only 25 of 31 patients changed from observation to prompt surgery did in fact have appendicitis. Among those initially planned for surgery, 7 would have been shifted to discharge or observation, all without actual appendicitis, and 5 patients would have still incorrectly been sent for prompt surgery.

Phase 2 Study

This was an open label, 2 site study (but predominantly a single site; 49 patients at site A; 7 at site B). Entry criteria were not as explicitly well developed as for the phase 3 study, but were intended to select patients with uncertainty as to appendicitis diagnosis, who were 8 years of age or older. Upon entry the referring surgeon was to complete a questionnaire specifying the intended management for the patient and the perceived likelihood of appendicitis. The patients were administered NeutroSpec and scanned at appropriate timepoints. The referring surgeon was again asked to identify the intended patient management. The scans were evaluated on site, but were also subsequently evaluated by 3 blinded readers; the blinded reader evaluation was deemed the primary reading for purposes of study outcome.

The 56 patients enrolled at this study, ranging in age from 9 to 77 years old, closely divided between male and female. Ultimately half of these patients were classified as appendicitis, half as not acute appendicitis. This is in contrast to the 30% rate of appendicitis in the Phase 3 study, and related to the revised and improved entry criteria that were employed in the phase 3 study. There were 7 patients who did not have appendicitis, but ultimately diagnosed with an infection of some (other) type.

The primary performance, based upon the aggregate of the 3 blinded readers, is shown below:

Phase 2 Study Primary Results					
Agreement	N	True Positive + True Negative	Agreement Percentage	95% C.I.	
	56	44	79	65	88
Sensitivity	N positive	True Positive	Sensitivity	95% C.I.	
	28	25	89	71	95
Specificity	N negative	True Negative	Specificity	95% C.I.	
	28	19	68	48	82
Positive Predictive Value	True Pos + False Pos	True Positive	PPV	95% C.I.	
	34	25	74	55	86
Negative Predictive Value	True Neg + False Negative	True Negative	NPV	95% C.I.	
	22	19	86	64	94

Inter-reader concordance between pairs of the 3 readers ranged from 77% to 80%; kappa statistics from 0.34 to 0.44.

The on-site readers had slightly better performance than the blinded readers on all parameters; agreement 88%, Sensitivity 96%, specificity 79%, PPV 82%, NPV 96%.

With regards to changes in planned management among the 56 patients related to the scan, 2 patients who reportedly would have been sent home immediately in the absence of the scan, would have been sent to surgery in light of the scan results, and did indeed have appendicitis. There would have been 13 patients changed from observation to discharge home; none actually having appendicitis, while 16 planned observation patients would have gone to immediate surgery, although only 15 of these actually had appendicitis in the final diagnosis. There were also 2 patients who would have gone to surgery absent the scan, who would have been appropriately discharged home in light of the scan result. Thus, no patients would have been inappropriately sent home, and the greatest impact was on patients being kept for observation who were mostly correctly shifted to discharge or surgery categories.

Pediatric Patients

Pediatric patients were pooled between the two studies to improve patient numbers. There were 15 patients age 5-9 yo; 48 patients age 10-17 yo. The performance characteristics in both of these subsets was generally similar to the studies overall.

Geriatric Patients

Patients of age >65 yo were also pooled between studies, for a total of 12 subjects. This small subset did not suggest significant loss of performance characteristics of the product.

Clinical Safety

The total safety experience with NeutroSpec consists of 523 people (patients and a limited number of healthy volunteers) exposed in 14 trials (407 patients in 11 studies conducted by Palatin). The majority of these additional trials were in other indications and early exploratory studies, and each enrolled modest numbers of patients. The Phase 2 and Phase 3 studies demonstrating efficacy enrolled 259 patients with potential appendicitis.

Patients ranged in age from 5 to 91 years old (median 52 yo). However there were only 29 between 5-11 yo, and 32 between 12-16 yo; there were 64 of age 65 yo or older.

Of the total group of patients, 37 reported an adverse event; 4 of these were severe (2 serious with fatal outcome). The two serious and fatal events were not likely related to the product (but cannot be excluded in 1 patient who developed hypotension 7 hrs after NeutroSpec administration); occurring in patients with significant pre-existing disease, and not in potential-appendicitis patients. Most of the other adverse events were classified as mild, 10 AEs were classified as moderate. Among AEs considered possibly related to the product there were 10 cases of flushing, 3 of dyspnea, and individual cases of other symptoms. The AE of flushing was the single most reported AE.

Group mean values of vital signs and laboratory parameters of white blood cell count, neutrophils, hemoglobin, total protein and BUN were noted to have small, and clinically insignificant transient shifts associated with administration of the product.

Immunogenicity was tested in limited number of patients (54) and did not demonstrate HAMA formation. However, the antibody assay is not validated, so that the meaning of this observation is uncertain. Similarly, in 30 patients who received a repeat injection of NeutroSpec, 5 patients exhibited positive HAMA responses; however the accuracy of this observation is dependent upon the unvalidated assay employed.

Advisory Committee

The results contained in the original submission were presented at a July 2000 meeting of the Medical Imaging Device Advisory Committee (MIDAC) who discussed the findings. The committee gave a recommendation that the company had demonstrated safety and efficacy of the product.

Special Populations

No studies have been performed in pregnant women, nor in nursing mothers.

The pediatric experience has not demonstrated any notable differences in efficacy or safety between pediatric patients and adult patients, but is limited by the size of the pediatric population studied (see Safety section). However, dosimetry should be re-evaluated in this population.

Among the 54 geriatric patients, no indication of an alteration in safety was observed.

Trade Name Review

Palatin initially proposed the trade name of "LeuTech" for this product. The Division of Medication Errors and Technical Support in the Office of Drug Safety advised against use of this name [REDACTED] (b) (4)

Palatin subsequently submitted NeutroSpec as a proposed trade name, to which DMETS and DDMAC had no objections. Consequently, the name NeutroSpec was adopted.

Recommendation

Based upon the safety and clinical imaging performance characteristics of this product, NeutroSpec is recommend for approval for scintigraphic imaging of patients with equivocal signs and symptoms of appendicitis who are 5 years of age or older.

This approval should be contingent upon agreement to a number of clinically-related Phase 4 Commitments:

- a) Evaluation of the performance of the product in neutropenic patients.
- b) Evaluation of dosimetry of pediatric patients.
- c) Validation of the existing antibody assay (or development of a new, and validated assay if needed) and evaluation of antibody formation following NeutroSpec administration in a sufficient number of patients to detect a true HAMA rate of 10% or greater if present.

There are also a number of CMC related PMCs that should be requested, as described in the review of Dr. Chana Fuchs.