

COMBIDEX

Compiled by Charles (Chuck) Maack, Prostate Cancer Advocate/Mentor

In not having Combidex approval in the U.S., our country's health system is missing an excellent method to distinctly identify and pin-point lymph node involvement of prostate cancer. Pioneered by Jelle Barentsz in Nijmegen, The Netherlands, Combidex consists of iron-oxide containing nanoparticles. When this contrast agent is administered intravenously, it is taken up by macrophages and transported to healthy lymph tissue. The iron causes changes in the magnetic characteristics of the tissue that result in low signal intensity on MR images. Therefore, 24 to 36 hours after Combidex injection, healthy lymph nodes are black on MR images due to the iron within macrophages. Macrophages are absent in lymph nodes with metastasis, and thus these lymph nodes do not have a low signal: the tissue is white. A more comprehensive description of Combidex is here

<http://tinyurl.com/ykqu8rr>

Combidex has been found to serve in many areas of diagnostics. See:

<http://tinyurl.com/yjxkymc>

An internet search of "Combidex" can provide additional information. Unfortunately, the FDA failed to give approval a few years back.

You can read of the experience of PC patient Dan Palmieri when he chose to travel to the Netherlands for Combidex imaging. He outlines not only the procedure and results, but provides a very comprehensive explanation/description of who you should contact, travel arrangements, expenses, and how to navigate your way around from arrival by air to subsequent train to local taxi service.

DVD:

<http://home.att.net/~ustoolombard/Combidex.ppt>.

HTML (NOTE: You will find some repetition in this copy, so please just ignore):

<http://tinyurl.com/yh9xcaq>

Several Medical Oncologists specializing in research and treatment of prostate cancer are proponents of this procedure when there is reasonable evidence that the lymph nodes may

have been compromised, and often recommend the procedure. Obviously the procedure would be a boon to imaging if available here in the United States, but without FDA approval, the only recourse is a trip to the Netherlands which is likely beyond the financial means of most patients.

Important as of March 2010, Combidex imaging is currently no longer available as explained below. This is such an important procedure that we hope that with our support Dr. Barentsz will be successful in return of manufacture of the contrast agent necessary to again provide this imaging.

To all patients who have traveled to the Netherlands for Combidex imaging; to all physicians who have referred patients and supported the importance of this imaging; and to all others having studied and recognize the importance of this procedure:

Having heard rumor that availability for the Combidex procedure was going to be cancelled, I sent an email to Dr. Jelle Barentsz, to confirm if this was true. Below is Dr. Barentsz reply and below that I have copied and pasted the attachment he sent to explain and request support of former patients, supportive physicians, and supportive prostate cancer organizations for his plan to revive production of the contrast agent for Sinerem/Combidex. Many of you will likely receive Dr. Barentsz personal email in the near future.

Please note in the attached the necessity that Dr. Barentsz receive email support for his intended effort to have the contrast agent for Sinerem/Combidex production continued to be used in trials to confirm the effectiveness of this procedure. He will also be seeking financial support in the future. Unfortunately, Combidex imaging will not be available in the foreseeable future until such time he is successful in his efforts for a return of production and a program developed for its continued use.

Accordingly, if you are a patient who has traveled to the Netherlands for Combidex imaging, or if you know of such patients and can pass this on to them, and if you are a physician or organization that has supported Combidex imaging, PLEASE arrange to send an email to Dr. Barentsz (J.Barentsz@rad.umcn.nl) identifying yourself as either a

patient, physician, or otherwise supportive individual for Sinerem/Combixel to be approved for continued manufacture for the purposes described by Dr. Barentsz below.

Charles (Chuck) Maack/Prostate Cancer Advocate/Mentor

Wichita, Kansas Chapter, Us TOO

Biography: <http://www.ustoowichita.org/leaders.cfm?content=bio&id=1>

Email: maack1@cox.net

Chapter Website "Observations": <http://www.ustoowichita.org/observations.cfm>

From: J.Barentsz@rad.umcn.nl [mailto:J.Barentsz@rad.umcn.nl]

Sent: Tuesday, March 23, 2010 6:49 AM

To: maack1@cox.net

Subject: RE: Combixel for patients from the U.S.

Dear Dr. Maack,

Yes I confirm. There is no contrast anymore anywhere in the world, because AMAG pharma decided to stop the production 5 years ago. Combixel MRI stops next week on April 1st.

I am working on solutions. I hope this will work. One of these days I am sending out the attached letter to all patients who have been here for a Combixel MRI.

Please give me your suggestions and comments on the strategy I point out in my letter.

Kind regards,

Jelle Barentsz

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Dear Mr. ..,

How are you? I am writing this letter to you to ask for your involvement to ensure that a major advance in the evaluation of men with PC (prostate cancer) is not lost. I am speaking about Combidex, which is also known as Sinerem in Europe. Combidex is the iron nanoparticle that is used as a contrast agent when combined with MRI (magnetic resonance imaging). You may hear or read about this as Combidex, Sinerem, or Ferumoxtran-10. The early papers on this agent also referred to it as USPIO (ultrasmall superparamagnetic iron oxide). So simply put, Combidex is the iron nanoparticle that enhances the ability of MRI to detect spread of PC to the lymph node. Unlike CT scans of the abdomen and pelvis which have a sensitivity of about 47%, Combidex has a sensitivity of 92% (only 8% false negatives) compared to 53% false negative reporting with CT. How can we afford to lose this important advance that is used to determine the patient's status and thus his treatment?

Some facts:

In March 2005 the FDA decided not to approve Combidex as a lymph node contrast agent. AMAG pharma (at that time Advanced Magnetics) then decided to stop further approval efforts, and to wait to see how successful Guerbet would be in Europe with their approval trial. AMAG pharma was the only producer of Combidex, and gave Guerbet the license for Combidex in Europe. The contrast was shipped to Guerbet, who then distributed the agent in Europe as Sinerem.

A few year ago AMAG decided to stop the production of Combidex. Guerbet had hoped that their appeal to the EMEA (European FDA) would be positive, so that they could start the production of this agent in Europe based on commercial income. However, in December 2007 the EMEA stated that a main study to evaluate the benefit-risk profile of the medicine had failed to statistically demonstrate the efficacy of Sinerem in the central reading. An appeal of Guerbet to re-evaluate the data was rejected recently. As a consequence Guerbet decided in December 2009 , based purely on financial reasons, not to continue efforts in Sinerem.

This means that no Combidex/Sinerem is produced anymore, and that further efforts for approval are cancelled. On April 1 of 2010, the last available batch of Combidex/Sinerem expires. That means that despite approval by the Dutch authorities, as of April 1st I will not be able to perform Combidex MR exams anymore.

What's new?

Recently AMAG pharma developed a new USPIO agent “ferumoxytol”, which is FDA approved for therapeutic use in patients with severe anemia, but NOT APPROVED for diagnostic use. It is possible that ferumoxytol may have lymph node enhancing properties similar to Sinerem (Combidex). However, there have been no published studies to clarify the optimal dose and time interval of MR imaging after injection of this agent, nor has the accuracy in detecting lymph node metastases been determined. Certainly these studies are mandatory before this agent is considered for widespread use in nodal staging. However, these studies will require a substantial amount of time if they are to be performed properly: the doses and the optimal imaging window need to be assessed, and the results using surgical dissection and follow-up validated. In my estimation, this will require at least a minimum of two to three years. A comparative study between ferumoxytol and Combidex, which I am willing to coordinate and perform, may speed up this process.

In the time that it will take for ferumoxytol to be evaluated and validated for patients with prostate cancer, it is necessary that men with PC have access to refined nodal staging with Combidex. This opinion is supported by your most prestigious treating physicians involved in PC evaluation & management, as well as their professional organizations in the USA and Europe. Although it is not a desirable situation, I could help having this test made available in the Netherlands, but resorting to this last resource makes me highly uncomfortable. Therefore, I am in discussion with Dr. Pereira, CEO of AMAG pharma, to help me solve this undesirable situation.

Solution:

The CEO of the Dutch authorities, the Dutch EMEA representatives, and the Department of Pharmacology at Radboud University Nijmegen Medical Center advised me to ask AMAG pharma for permission to use the preclinical, toxicology and safety data and documents of Sinerem/Combidex to apply for non-commercial production of this agent. After obtaining this approval, I can produce Combidex within one year. As the safety, toxicology and pre-clinical data are excellent, our Ethical Committee and the Dutch authorities allow me to use this agent on patients on a scientific basis. This also may open the way to start combined scientific trials with US and European participants, not only in prostate but also in other cancer types. Therefore, the use of Combidex will be more widespread.

In addition, trials need to be initiated to explore and validate ferumoxytol for use as a nodal contrast agent, which will lead to FDA approval. Together with some of my expert US partners I am willing to help design coordinate and perform these trials.

I firmly believe that continuing with Combidex will not only allow patients to have recourse to a superior staging examination to determine lymph node involvement, but will additionally allow on-going data acquisition to facilitate evaluation of the new agent ferumoxytol.

What do I need from you?

Your help is very important. You are part of a powerful network. Many of you, and your friends and/or family may be able to help by putting political, economical, PR, and moral pressure on AMAG pharma. Please see how you can mobilize your network and focus on our goal to get the license from AMAG pharma. I would like to form a Combidex Patient

Group (CPG), who working together with me and with your referring physicians will coordinate and optimize your “patient power”. At short term representatives from this group: treating physicians, patients, leaders from patient advocacy groups, leading politicians, leaders of industry, representatives from NIH/NCI, etc need to show Dr. Peirera the importance for patients of the continuation of Combidex.

- Can you please send me an e-mail telling me, in what way you can help my goal in having Combidex/Sinerem available within the next year?

In addition, I need funds to get the license from AMAG, to produce Combidex/Sinerem on a non -commercial basis, and to perform international scientific trials. My estimate is \$2,000,000 in total. Although I cannot guarantee this right now, I expect that this investment will be paid back through by the MR exams, and by the international trial participants. Can you please indicate if you are willing to give financial support, and if so in what way you like to contribute?

To enhance the importance of the patients’ perspective and demonstrate this to Mr. Pereira, I ask you to tell me in a few lines how Combidex changed your treatment, and what it meant to you and your family & friends. Please send this letter in an e-mail as a Word file attached, before April 19, as I will have a meeting with Dr. Pereira and his AMAG-team on April 22nd.

- Can you please send me such a letter *before April 19th*?

Finally, in order to promote lymph node imaging with Combidex, Dr. Roach and I are planning a meeting on Lymph Node Positive Prostate Cancer on 9/26/10 in San Francisco. Patients are also invited and we would like to include a patient panel as part of the program.

I know that together we will help Combidex to survive!

Kind regards,

Jelle Barentsz, MD, PhD.