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Statistical Review and Evaluation Clinical Studies

NDA/BLA Number: 018511 s28

Drug Name: DRAXIMAGE DTPA

Proposed Indication(s): Technetium Tc 99m Pentetate Injection for (b) (4)

Applicant: Jubilant DraxImage Inc.

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1. EXECUTIVE SUMMARY

FDA approved **DraxImage DTPA Kit for the Preparation of Technetium Tc99m Pentetate** in 1989 for **intravenous injection** use to perform kidney imaging, brain imaging, to assess renal perfusion, and to estimate glomerular filtration rate. The sponsor submitted this sNDA based on a literature search, review, and analysis and stated that no prospective nonclinical or clinical studies were required to support the sNDA application per several discussions/meetings with FDA. The sponsor proposed the following new indication through 505(b)(2) pathway:

- **Technetium Tc 99m Pentetate Injection for** [REDACTED] (b) (4)

In support of the indication, the sponsor submitted the efficacy results inherent in publications. These studies are exploratory, lack a truth standard, are small in sample size, lack quantitative information and statistical evidence. There is a potential bias in studies with angiographic truth standards and weakens detailed assessment of performance. The procedures used to conduct the studies and assess the images were not standardized across the studies. Unbiased assessment of performance with available data cannot be confidently determined.

A summary is given below:

- Study 1(Trujillo, 1997): 99mTc-DTPA/99mTc-MAA V/Q scintigraphy coupled with specific diagnostic criteria is informative as an adjunct procedure in diagnosing suspected PE.
- Results of study 1 supported by smaller studies by Frietas et al. (1995), Selby et al. (1990) and Lear et al (1996).
- The agreement between Aerosol perfusion and Xe-133 perfusion was 82 % (202/245) and the agreement between Aerosol perfusion and Kr-81 perfusion was 80% (79/99).
- 1983 NRC Final Rule allowed use of aerosolized Tc99m DTPA off-label for ventilation studies by licensed practitioners resulting in the long history of extensive off-label clinical use of Tc99m-DTPA. Sponsor estimates over [REDACTED] (b) (4) ventilation scans were performed with aerosolized Tc99m DTPA over last 30 years.
- 21,633 subjects exposed to inhaled Tc99m DTPA exposure in 389 clinical studies including over 825 pediatric subjects. No adverse events reported in these publications
- Sponsor estimates over [REDACTED] (b) (4) ventilation scans performed with Tc99m DTPA in U.S. since 2005. Adverse events in 5 separate subjects were reported to sponsor since 2005 for Tc99m DTPA inhaled during ventilation scan

Inference:

The quantitative information extracted from the published papers is weak to support the proposed indication.

2. INTRODUCTION

Jubilant DraxImage Inc.(JDI) submitted this sNDA based on a literature search, review, and analysis and stated that no prospective nonclinical or clinical studies were required to support the sNDA application per several discussions/meetings with FDA. The sponsor stated that the data could not be pooled because the procedures used to conduct the studies and assess the images were not standardized across the studies. Therefore, no formal meta-analysis could be performed.

2.1 Overview

FDA approved **DraxImage DTPA Kit for the Preparation of Technetium Tc99m Pentetate** in 1989 for **intravenous injection** use to perform kidney imaging, brain imaging, to assess renal perfusion, and to estimate glomerular filtration rate.

New Indications Proposed by Sponsor through 505(b)(2) sNDA

Technetium Tc 99m Pentetate Injection for [REDACTED] (b) (4)

2.1.1 Regulatory History

DTPA was approved in the US in 1989. However, in 2006, the NDA was transferred from Merck Frosst to DraxImage and sold in the US under the name of DRAXIMAGE® DTPA which, is currently approved only for intravenous injection use. Inhaled Technetium Tc 99m Pentetate has been used to image the lung for over 30 years.

Aerosolized Tc99m DTPA: Extensive History of Off-label Use

- 1983 NRC Final Rule
 - Allowed use of aerosolized Tc99m DTPA off-label for ventilation studies by licensed practitioners
- Sponsor estimates over [REDACTED] (b) (4) ventilation scans were performed with aerosolized Tc99m DTPA over last 30 years

In the current submission, JDI presented a proposal towards the approval of the 505(b)(2) efficacy supplement application based on a literature review and the available information. In preparation for the submission of this supplement:

- April 20, 2015: Sponsor met with the Agency under Pre-IND 125711 to discuss a 505(b)(2) application for Technetium Tc 99m Pentetate administered by inhalation for imaging the lung using extensive literature review and the available information to support the proposed indication.

- December 18, 2015, iPSP agreement was reached for Literature based NDA without prospective clinical or nonclinical studies.
- May 17, 2016: pre-NDA meeting: Agreed on literature search process and appropriate comparators
- February 27, 2017: NDA Submission

2.2 Data Sources

Summary datasets as published in papers were provided in SAS xpt format. Definition files were provided.

EDR Location: <\\CDSESUB1\evsprod\NDA018511\018511.enx>

3.1 Data and Analysis Quality

Primary endpoints were different across published papers. Procedures used to conduct the studies and assess the images were not standardized across the studies. No new clinical data were submitted for review.

3.2 Evaluation of Efficacy

3.2.1 Study Design, demographics, baseline characteristics

Study design(s), demographics, baseline characteristics etc. were limited to papers as reported in the published literature.

3.2.2 Number of studies

A total of 389 clinical studies (6 pharmacokinetics and ADME studies, 362 prospectively designed clinical studies and 21 retrospective clinical studies), 46 case reports, 56 review articles, 17 editorials, and 11 guidance documents were considered relevant. Sponsor included a summary of 7 studies in their version of label in section 14.

3.3 Results and Conclusions

This submission was based on studies from literature search. There were no prospective clinical studies included in the submission. The literature search resulted in several useful studies, but the procedures used to conduct the studies and assess the images were not standardized across the studies. The sponsor identified seven studies and included their summaries in their proposed label (section 14). The clinical and statistical team found these papers lacking quantitative information in support of the proposed indication. The team reviewed several other papers and found some publications that may extend support to a modified version of the proposed indication.

The clinical team stated that the publications involving V/Q scanning for pulmonary embolism are the strongest. Among them, the best study is Trujillo et al. 1997 which compares V/Q scans to angiography in 455 subjects. There are supportive studies using an angiography or autopsy truth standard such as Freitas et al., 1995, Selby et al., 1990 and Lear et al., 1996.

Another strong study that looks at agreement between V/Q studies performed with Tc99m-DTPA and approved comparators Xe-133 or Kr-81m in 107 subjects is Alderson et. al., 1984. Similar but smaller studies looking at agreement between Tc99m-DTPA and Xe-133 or Kr-81m are Finn et al., 1986 and Ramanna et al., 1986.

The results of these publications are given below.

3.3.1 Publication Trujillo, et al (1997): Lung Scan

Ref: Trujillo NP, Pratt JP, Talusani S, Quaife RA, Kumpe D, Lear JL. DTPA aerosol in ventilation/perfusion scintigraphy for diagnosing pulmonary embolism. *J Nucl Med.* 1997 Nov; 38(11):1781-1783.

This publication compares V/Q scans to angiography in 455 subjects. Truth standard was angiography or autopsy. There was a single reader (Lear criteria). The details as provided in the publication are given below:

Patients:

All patients for whom lung scan was requested for evaluating suspected PE between Sept 1, 1997 and August 31, 1997 were eligible for the study. Patients were excluded if they failed to complete the full examination (ventilation scan, perfusion scan and chest radiograph).

Lung Scintigraphy – Performed perfusion imaging, ventilation scan, & chest radiograph obtained. The criteria for evaluating Ventilation/ Perfusion scans using Technitium-99m-DTPA and Technitium-99m-DTPA were:

Normal – no significant perfusion defects

Low - (i) Matched perfusion defects and normal chest radiograph,
(ii) Matched perfusion defects and normal chest radiograph,
(iii) Nonbasilar matched perfusion defects and chest radiograph abnormally larger in size than perfusion abnormality,
(iv) Nonsegmental perfusion defects caused by either artifact or small pleural effusion.

Intermediate – Segmental matched perfusion defects and chest radiograph showing infiltrate, atelectasis or effusion.

Medium - One moderate defect to two segmental equivalent defects that are mismatched.

High - More than two segmental equivalent perfusion defects that are mismatched (in at least two noncontiguous areas)

The lungs were interpreted by prospectively applying above criteria developed for this technique. Each scan was interpreted by a nuclear medicine physician (one of three interpreters during the study) and classified as normal, low probability, intermediate probability, medium/moderate probability or high probability. This interpretation was used as the final result in the study.

Pulmonary Angiography

Patients were referred for pulmonary angiography based on clinical suspicion for PE as determined by the ordering physician (with the knowledge of the results of the lung scan). Angiographic results obtained within 2 days of V/Q scan were classified as either positive or negative for PE by the angiographers performing the studies (inconclusive or delayed angiographers were not included in the study). Bilateral angiography was performed in all patients unless PE was found in the first lung studied.

Results:

5162 V/Q scans attempted of which 5017 scan were eligible for analysis
Decision to perform angiography based on V/Q scan and clinical information (potential bias)
Scans were performed: 2467 inpatient scans (48%) and 2550 outpatient scans (52%)
n=455 angiography studies on adults (out of n=5017 V/Q scans)
2146 scans on male patients - mean age 52 ± 18 yrs.
2871 scans on female patients - mean age 48 ± 16 yrs.

Scan interpretation:

Normal in	805 scans (16%)
Low probability in	2710 scans (54%)
Intermediate probability in	543 scans (11%)
Medium probability in	500 scans (10%)
High probability in	459 scans (9%)

The following table shows the extent of potential bias in the obtaining the truth standard of angiography.

Table 1: Angiographic Results in Various Lung Scan Interpretations*

Lung scan interpretation	Frequency of angiography	# of pulmonary angiography performed	# (%) of negative angiography	# (%) of positive angiography
Normal	< 1%	3	3 (100%)	0 (0%)
Low 95% CI	4%	111	103 (93%) (3, 14)	8 (7%)
Intermediate 95% CI	21%	114	85 (75%) (18, 34)	29 (27%)
Medium 95% CI	30%	149	86 (58%) (34, 51)	63 (42%)
High 95% CI	17%	78	6 (8%) (84, 97)	72 (92%)
Total		455	283 (62%)	172 (38%)

* Source: Publication Trujillo, et al (1997): Lung Scan

Table 2: Sensitivity and Specificity - Exploratory Analyses*

Test	PE present	PE absent
Table 1 + (high)	72	6
- (low)	8	103
Total – Table 1	80	109
Sensitivity (95% CI)	90% (81, 96)	
Specificity (95% CI)	94% (88, 98)	
Table 2 + (high)	72	6
- (low + Intermediate)	37	188
Total – Table 2	109	194
Sensitivity (95% CI)	66% (56, 75)	
Specificity (95% CI)	97% (93, 99)	
Table 3 + (high)	72	6
- (low + Intermediate + medium)	100	274
Total – Table 3	172	280
Sensitivity (95% CI)	42% (34, 50)	
Specificity (95% CI)	98% (95, 99)	
Table 4 + (high + medium)	135	92
- (low + Intermediate)	37	188
Total – Table 4	172	280
Sensitivity (95% CI)	78% (72, 84)	
Specificity (95% CI)	67% (61, 73)	

*Source: Derived from the information in Table 1

3.3.2 Publications Supporting Angiography/Autopsy Studies

- Freitas et al., 1995
 - **n=133** subjects with angiography
 - **PE present in 2 of 36 low, 5 of 6 high, 29 of 91 intermediate**
- Selby et al., 1990
 - **n=72** subjects with angiography or autopsy

- **PE present in 2 of 31 normal/low, 24 of 25 high, 5 of 16 intermediate**
- Lear et al., 1996
 - **n=33** subjects with angiography
 - **PE present in 0 of 7 low, 7 of 8 high, 0 of 1 normal, 4 of 7 indeterminate, 4 of 10 medium**

3.3.3 Publication Alderson et al., 1984: Comparator Agreement

Ref: Anderson P O et al. Tc-99m-DTPA Aerosol and Radioactive Gases Compared as Adjuncts to Perfusion Scintigraphy in Patients with Suspected with Pulmonary Embolism, Radiology 1984; 153; 515-521.

The clinical utility of Technetium Tc 99m Pentetate Injection for inhalation was evaluated in 107 patients with suspected pulmonary embolism. The inhalation images with perfusion scans and chest radiographs were compared to $^{133}\text{Xenon}$ (FDA approved – in common use) and $^{81\text{m}}\text{Krypton}$ (FDA approved – withdrawn in 2001 - short half-life for product and generator). The images were evaluated by independent reviewers. There were four readers, and total number of readings was 245.

All 107 patients received Technetium Tc 99m Pentetate Injection, 81 patients received $^{133}\text{Xenon}$, and 26 patients received $^{81\text{m}}\text{Krypton}$. The average age of the patients was 62 years (range 20 to 91 years). There were 58 women and 48 men. The most common symptoms at baseline were chest pain (n = 62, 58%) and dyspnea (n = 51, 48%).

The author stated that the agreement between Aerosol perfusion and Xe-133 perfusion was 82 % (202/245) and agreement between Aerosol perfusion and Kr-81 perfusion was 80% (79/99).

3.4 Pediatric Subjects:

- Pediatric literature is more limited than adult literature
- No PE clinical studies appear to involve children
- 9 clinical studies involved V/Q matching for pneumonia, unilateral hyperlucent lung, scoliosis
- 1 lung structure pediatric clinical study (Scoliosis)
- 23 ventilation distribution clinical studies included at least some children (Pneumonia, asthma, cystic fibrosis, primary ciliary dyskinesia)
- 26 alveolar permeability clinical studies included at least some children (asthma, HIV, interstitial lung disease)
- Additional pediatric case reports

3.5 Evaluation of Safety

Safety: Literature

- **21,633 subjects** exposed to inhaled Tc99m DTPA exposure in 389 **clinical studies**
 - Includes over 825 pediatric subjects
- **No adverse events** reported in these publications
 - Only 26 of 389 studies included a safety statement (1,287 subjects)
 - Unclear what safety parameters were assessed

Safety: Post marketing

- Sponsor estimates over ^{(b) (4)} ventilation scans performed with Tc99m DTPA in U.S. since 2005
- adverse events in 5 separate subjects reported to sponsor since 2005 for Tc99m DTPA **inhaled** during ventilation scan
- One report of a **single death** in 2015 following **inhaled** Tc99m DTPA during V/Q scan
 - 60 year old. male reported SOB approximately 5 minutes after administration
 - Progressed to **anaphylactic shock** and cardiac arrest
 - Death 4 weeks later in ICU
 - Causal relationship between drug and event suspected by reporter
- Safety: no adverse events reported through literature, sponsor, or FAERS for inhaled Tc99m DTPA in pediatric patients.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

A comparison of results in sub-populations or special groups was not included in the submission.

5.1 Statistical Issues and Collective Evidence

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