

Convetra, Inc.

Canine OA Pain Management Market: 2 Major Gaps



Daily Drugs

- Ineffective for many
- Long-term safety issues
- Poor compliance

General Practices



Joint Replacement

- Not for all joints
- High risk for older pets
- Disruptive rehab

Specialty Hospitals

Therapeutic Gap
No durable, proven
intermediate treatment options

\$4.2B Veterinary Revenue Gap
~2M cases / year referred
only ~0.6M treated¹



OA and Synovial Macrophages

The role of synovial macrophages and macrophage-produced cytokines in driving aggrecanases, matrix metalloproteinases, and other destructive and inflammatory responses in osteoarthritis

Bondeson J, Wainwright SD, Lauder S, et. al. Arthritis Research & Therapy 7 2006

8:R187(doi:10.1.186/ar2099)

- Synovial inflammation is implicated in many signs and symptoms of OA, including joint swelling and effusion
- In the osteoarthritis synovium, both inflammatory and destructive responses are dependent largely on macrophages and these effects are cytokine driven through a combination of IL-1 and TNF α
- These cytokines can stimulate their own production and induce synovial cells and chondrocytes to produce IL-6, IL-8, leukocyte inhibitory factor; as well as stimulate protease (matrix metalloproteinases (MMPs) and aggrecanases) and prostaglandin production
- ❖ **“Results suggest prioritization of attempts to modify macrophage function in OA, with the aim of decreasing both inflammatory synovitis and the production of degradative enzymes (cytokines) of importance for the progression of the disease”**



What is radiosynoviorthesis (RSO)? Intra-articular injection of radioisotope (radionuclide) to treat joint inflammation

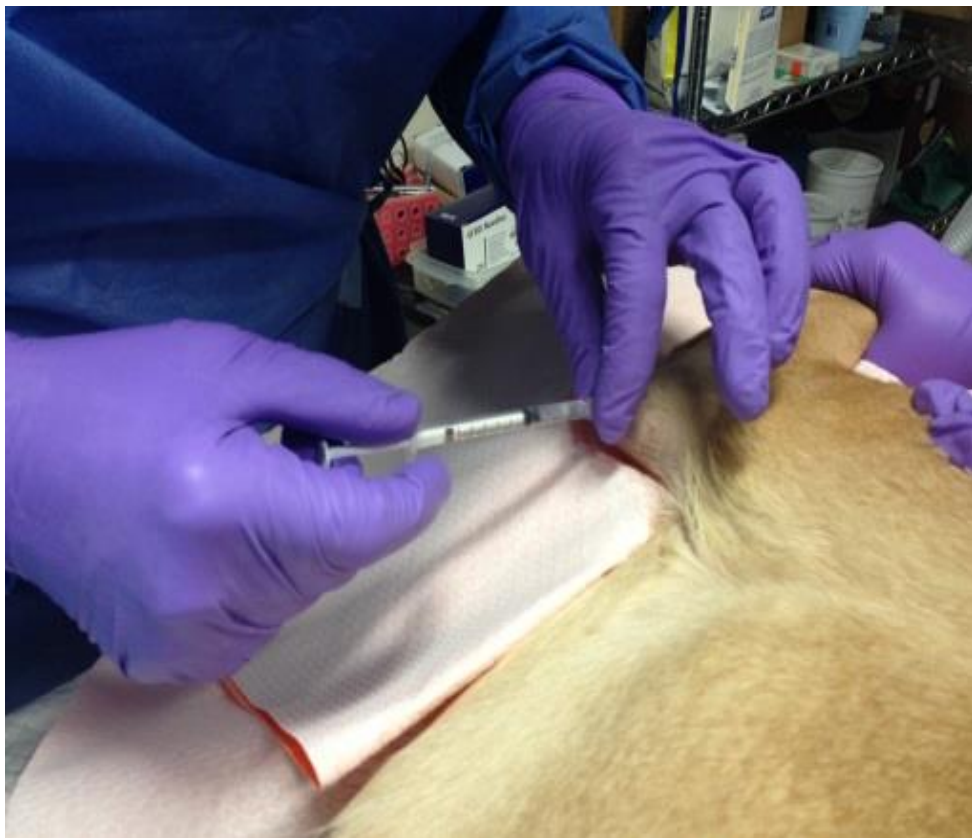
Mode of action: Radionuclide is absorbed by synoviocytes and phagocytized by macrophages within the synovium resulting in apoptosis and non-inflammatory ablation of inflammatory cells

The homogeneous tin colloid suspension (1.5 – 20 μm) of tin-117m emits discrete (0.3 mm radiation range), low-energy conversion electron radiation

The colloid containing micro particles is retained in the canine joint space for at least 42 days (3 half-lives)

Mechanism of cell death from Synovetin OA is from extended duration ($T_{1/2} = 14\text{d}$) low energy radiation (<158 keV) exposure effects

How Safe is Synovetin OATM in Canines?



✓ Cumulatively 100 elbows of 75 dogs injected

- Examined multiple times post-treatment over 12 months
- PE, CBC, Chem screen, UA, Joint fluid, lameness, range of motion, limb circumference, force plate, MRI, PET, CT, radiographs, Brief Pain Inventory, Colorado chronic pain scoring, concomitant meds, radiation, scintigraphy modalities were used
- 3 sites LSU, MU veterinary schools and Gulf Coast Veterinary Specialists in Houston
- No safety associated parameters fell outside of expected norms (including a mis-administration)



Clinical Studies Trialing Synovetin OA



Canine				
Study name	Study Number	Date Injected	Number Evaluated	Site
5 normal dog safety study	None assigned by University of Missouri	March 31, 2015 to May 15, 2015	5 (5 elbows)	University of Missouri College of Veterinary Medicine, J. Lattimer DVM, DACVR
Grade 1 & 2 elbow OA client dog study	None assigned by University of Missouri	October 14, 2015 to last dog evaluated Feb. 27, 2017	44 (46 elbows)	Gulf Coast Veterinary Specialists, M. Fabiani, DVM, DACVR; C. Hudson DVM, DACVS, B. Beale DVM, DACVS Louisiana State University School of Veterinary Medicine, K. Aulakh, DVM, DACVS University of Missouri College of Veterinary Medicine, J. Lattimer DVM, DACVR
Grade 3 elbow OA client dog study	C-22017	June 21, 2017 to July 26, 2017	15 (27 elbows)	GCVS, Houston, TX LSU-SVM, Baton Rouge, LA
Re-injection of 117m Sn colloid (Synovetin OA) in grade 1 or 2 client dog study	C - 80817	September 11, 2017 to October 13, 2017	10 (20 elbows)	LSU-SVM, Baton Rouge, LA MU-CVM, Columbia, MO

Studies C-22017 and C-80817 are GMP, GCP and GDP pivotal studies validating commercially produced Synovetin OA™ and the commercial manufacturing process utilizing Theragenics, Inc. a human medical radioisotope manufacturer based in Buford, GA (NE of Atlanta)



How Effective is Synovetin OA?



✓ **Canine Brief Pain Inventory**

- Client survey about reduction in pain and level of activity
- Each time point survey compared to baseline survey results
- 37 dogs initially treated with the label dose of Synovetin OA

✓ **3 month results**

- 15/37 (40%) both pain AND level of activity improved successfully (conventional cBPI success)
- 24/37 (65%) one OR other improved successfully with NO worsening of the other (client success)

✓ **6 month results**

- 14/35 (40%) both pain AND level of activity improved successfully
- 24/35 (69%) pain OR level activity improved successfully with NO worsening of the other



How Effective is Synovetin OA?



✓ **Canine Brief Pain Inventory**

- Client survey about reduction in pain and level of activity
- Each time point survey compared to baseline survey results
- 37 dogs initially treated with the label dose of Synovetin OA

✓ **9 months results**

- 20/32 (62%) both pain AND level of activity improved successfully
- 25/32 (78%) one OR other improved successfully with NO worsening of the other

✓ **12 months results**

- 16/31 (52%) both pain AND level of activity improved successfully
- 24/31 (77%) one OR other improved successfully with NO worsening of the other



How Effective is Synovetin OA?



- ✓ **Force plate analysis of Grade 1 or 2 elbow OA (single leg injection)**
 - 22 dogs with grade 1 or 2 elbow OA in which the most painful elbow was injected
 - $\geq 5\%$ positive change in PVF or VI considered a successful treatment effect
 - Each dog served as its own control comparing each time point to initial baseline data
 - 3 different dosages (1.0, **1.75** and 2.5 mCi per joint for 50 lb. dog)
 - 18/22 (82%) treatment effect at one or more time points
- ✓ **1 month** – 9/22 (41%) treatment success
- ✓ **3 months** – 13/22 (59%) treatment success
- ✓ **6 months** – 13/21 (62%) treatment success
- ✓ **9 months** – 11/18 (61%) treatment success
- ✓ **12 months** – 4/13 (31%) treatment success



How Effective is Synovetin OA?



- ✓ **Force plate analysis of Grade 1 or 2 elbow OA (elbow reinjection)**
 - 10 dogs with grade 1 or 2 elbow OA in which both affected elbows were injected
 - $\geq 5\%$ positive change in PVF or VI considered a successful treatment effect
 - Each dog served as its own control comparing each time point to initial baseline data
 - Label dosed (1.75 mCi per joint in a 50 lb. dog)
 - Baseline, 3 and 6 month force plate evaluations only
 - 6/9 (67%) treatment effect at one or more time points
- ✓ **3 months** – 5/9 (56%) treatment success
- ✓ **6 months** – 6/9 (67%) treatment success



How Effective is Synovetin OA?



- ✓ **Clinicians lameness assessment (single leg injected)**
 - Lameness grading from 0 – 5 (worst)
 - Evaluated at walk and trot before and after joint manipulation
 - Each dog served as its own control comparing each time point to initial baseline data
 - 34 dogs in the Per Protocol group
 - 3 different dosages (1.0, **1.75** and 2.5 mCi per joint for 50 lb. dog)
- ✓ **9 months** – changes from baseline, indicating improvement from baseline, were found to be statistically significant (n=18)
- ✓ **12 months** – changes from baseline, indicating improvement from baseline, were found to be statistically significant (n=19)
- ✓ **McNemars test** –the comparison of cBPI success to clinician-assessed lameness success comparing baseline to each visit indicated statistical agreement.



Mykonos Experience With Synovetin OA



- ✓ **Mykonos, 1.5 year old, castrated male, 88 lb. German Shephard, bilateral ununited anconeal prs.**
 - ✓ **Right elbow injected with label dose 10/14/15**
 - ✓ **Left elbow injected with label dose 9/20/16**
 - ✓ **Both elbows injected with label dose 12/18/17**

cBPI scoring	Baseline	1 mos.	3 mos.	6 mos.	9 mos.	Baseline ²	1 mos.	3 mos.
Date	10/13/15	11/10/15	1/7/16	4/1/16	7/7/16	9/19/16	10/26/16	12/15/16
Pain Severity Score (Q 1-4)	6.25	2.00	0.75	0.00	0.00	6.00	0.00	0.00
Pain Interference Score (Q 5-10)	2.17	0.83	0.00	0.33	0.00	7.17	0.00	0.00
Quality of Life Score (Q 11)	Good	Very Good	Very Good	Excellent	Excellent	Poor	Excellent	Excellent

Baseline prior to left elbow injected
Baseline² prior to right elbow injected



Mykonos Experience With Synovet[®] OA



- ✓ **Mykonos, 1.5 year old, castrated male, 88 lb. German Shephard, bilateral ununited anconeal prs.**
 - ✓ **Right elbow injected with label dose 10/14/15**
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	6 mos.	9 mos.	12 mos.	Baseline ³	3 mos.	6 mos.	9 mos.	12 mos.
Date	3/23/17	6/22/17	9/21/17	12/17/17	5/4/18	7/6/18	9/21/18	12/30/18
Pain Severity Score (Q 1-4)	0.00	0.00	0.00	0.75	0.00	0.00	0.00	0.00
Pain Interference Score (Q 5-10)	0.00	0.00	0.00	0.67	0.00	0.00	0.00	0.00
Quality of Life Score (Q 11)	Excellent	Excellent	Excellent	Very Good	Excellent	Excellent	Excellent	Excellent

Baseline³ prior to both elbows injected



Mykonos Experience With Synovetin OA

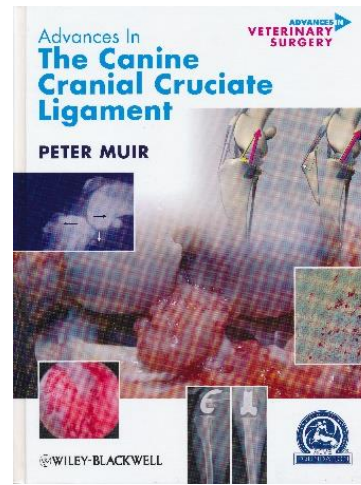




Synovetin OA Summary

- Tin-117m is a ***radiotherapeutic device*** with a unique mode of action that targets inflammatory cells which incite multiple inflammatory cytokinetic cascades. This device not only reduces pain, but also alters the progression of arthritis; hence, '***disease modifying***'. ('disease modifying' is intuitive based on mode of action; however, must be clinically validated in dogs)
- Due to its unique mode of action, tin-117m is not associated with the historical adverse drug events seen with NSAIDs: gastrointestinal, renal, platelet and hepatic
- Tin-117m provides veterinary specialty clinics another **revenue stream** through addressing arthritic dogs refractive to general 'standard of care' treatments

Studies in dogs with cranial cruciate ligament (CrCL) deficiency and rupture...



Evidence of Pre-Radiographic Synovitis

**Purdue University
Canine Study**

Synovial macrophage density was increased in all affected joints and associated with radiographic severity of OA and presence of pro-inflammatory cytokines

European Canine Study

CrCL mechanical strength was significantly reduced in animals with immune-mediated synovitis, and IL-8 expression was higher in CrCLs that ruptured in the subsequent 6 months

**University of Wisconsin
Canine Study**

Synovitis was significantly correlated with radiographic OA and was present in all CrCL joints that ruptured, as well as in all stable contralateral stifles

>\$1.32B/year is spent on ACL disease in the US (JAVMA 2005,227:1604-1607)

Synovitis is an early feature of arthropathy in dogs with minimally detectable damage

Sources: Klocke NW, et al. *Am J Vet Res*. 2005;66:493-499; Doom M, et al. *Vet Immunol Immunopathol*. 2008;125:143-161; Bleedorn JA, et al. *Vet Surg*. 2011;40:531-543.



Synovetin OA Next Steps

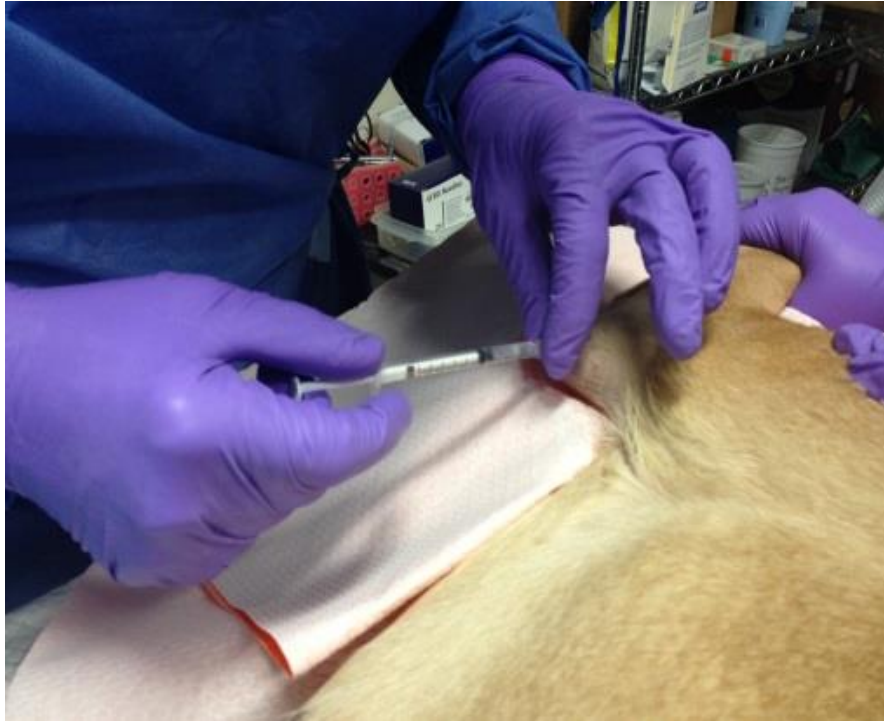


Figure: Canine elbow IA injection of tin-117m

Clinical Experience program:

- Convetra is recruiting 10 specialty hospitals to introduce Synovetin OA
- Profile of specialty hospital candidate
 - Surgeon(s) with an interest in sports medicine and rehabilitation
 - Gait analytics
 - Perform arthroscopy
 - Hospital has an existing RAM license (I-131 or Technetium)
 - Radiologist interested in nuc med
 - Searchable patient data base

Convetra will:

- Provide Synovetin OA to treat 3 dogs with elbow OA
- Support amending RAM license to add tin 117m
- Train RSO and Authorized Users

Thank you