Cummings Veterinary Medical Center AT TUFTS UNIVERSITY

Foster Hospital for Small Animals
55 Willard Street
North Grafton, MA 01536
(508) 839-5395

All Medical Records

Client:
Address: B6

Patient: B6
Breed: Doberman Pinscher
DOB: B6

Species: Canine
Sex: Male (Neutered)

Home Phone:
Work Phone:
Cell Phone: B6

Referring Information

B6

Client:
Patient: B6

Initial Complaint:
New cruciate evaluation, possibly sx at rDVM

SOAP Text Jul 8 2015 2:30PM - B6

7/8/2015 4:58:22 PM NEW VISIT

History: 7 yo CM Dobie presenting for his right hind limb lameness. 2 weeks ago he became acutely lame on his RH after running around. He was taken to the DVM who suspected a cranial cruciate ligament rupture. B6 rDVM did bloodwork, showed increase of ALT and started him on B6 ALT decreased after 2 weeks.

Exam:

B6

Client: B6
Patient:

B6

SOAP Text Jul 16 2015 9:30PM - B6

Subjective

Objective

Assessment

Plan

B6

7/17/2015 7:21:04 AM EXAM, GENERAL

B6

Client:
Patient: B6

B6

7/17/2015 8:08:32 AM

B6

7/17/2015 11:02:11 AM

B6

B6

*** 3 doses*** - Expires: 7/16/2016 No Refills

7/17/2015 6:40:43 PM
Prescribed B6

Client: B6
Patient:

Instructions - 3.8 mg IV q6 - Expires: 7/16/2016 No Refills

SOAP Text Jul 18 2015 8:08AM - B6

B6

Plan (P)
P1: Continue
P2: Continue
P3: Continue
P4: Feed q8,
P5: water , walk, HR, RR q4
P6: BW and Temp q12
P7: Discharge 7/19/15
P8: Move to B-ward

SOAP completed by: B6
SOAP reviewed by:

Prescribed B6
Instructions - Give 3.6 mg IV q6 - Expires: 7/17/2016 No Refills

SOAP Text Jul 19 2015 8:18AM - B6

7/19/2015 8:19:07 AM EXAM, GENERAL

B6

Client: B6
Patient:

B6

Plan (P)
P1: Discharge today
P2: Go home meds B6
P3: Go home meds

SOAP completed by: B6 16
SOAP reviewed by:

7/19/2015 8:26:05 AM

B6

7/19/2015 8:26:59 AM

B6

Initial Complaint:
Chief Recheck No Xrays

SOAP Text Oct 7 2015 3:13PM - B6

B6

Recheck examination:

Client: B6
Patient:

SOAP created by: B6 , V'16
SOAP reviewed by:

Initial Complaint:
New - B6 - DCM/arrhythmia (poss DCM study)

Initial Complaint:
Emergency

Initial Complaint:
B6 - CT on hold 12/11 @ 3PM
Hx VW and heart disease (cardio appt 12/5)

Initial Complaint:
Drop Off Chief Surgery, Admit to E B6

SOAP Text Dec 20 2018 9:28AM - B6

Subjective
EXAM, GENERAL

Subjective (S)

10 yo CM Doberman

B6

and it has since discontinued and the odor has returned B6 has a history of VWD and DCM which he is on medications to help manage.

Subective (S)

BAR, nervous
mild dehydration
MM pink, Crt 0.5 seconds

Client: B6
Patient:

Objective (O)

B6

H/L: NMA, NSR, FPSS. Normal BVS in all lung fields, no crackles or wheezes ausculted. Eupnic.

B6

Diagnostics Completed:

12/10/2018:

B6

Assessment (A)

A1: B6

A2: History of DCM

A3:

A4: B6

Plan (P)

P1: B6

SOAP completed by: B6 V'19

SOAP reviewed by:

Disposition/Recommendations

Cummings Veterinary Medical Center AT TUFTS UNIVERSITY

Foster Hospital for Small Animals
55 Willard Street
North Grafton, MA 01536
(508) 839-5395

Client:	B6
Veterinarian:	
Patient ID:	320320
Visit ID:	

Patient:	B6
Species:	Canine
Breed:	Doberman Pinscher
Sex:	Male (Neutered)
Age:	B6 Years Old

Lab Results Report

None **7/16/2015 10:03:39 PM** **Accession ID:** B6

Test	Results	Reference Range	Units
Blood Glucose - fee charged (TVETS)	B6	0 - 0	mg/dl
PCV for PCV/TS/AZO/BG		0 - 0	
TS (TVETS)		0 - 0	g/dl
AZO		0 - 0	mg/dl

None **7/17/2015 9:11:00 AM** **Accession ID:** B6

Test	Results	Reference Range	Units
VWF:AG	B6	0 - 0	%

None **7/17/2015 10:52:00 AM** **Accession ID:** B6

Test	Results	Reference Range	Units
SALINE AGGLUTINATION	B6	0 - 0	
BLOOD TYPE		0 - 0	

None **12/10/2018 1:54:00 PM** **Accession ID:** B6

Test	Results	Reference Range	Units
VWF:AG	B6	0 - 0	%

None **12/20/2018 9:22:02 AM** **Accession ID:** B6

Test	Results	Reference Range	Units
PLT(ADVIA)	B6	173 - 486	K/uL
PT		6.2 - 9.3	seconds
PTT		8.9 - 16.3	seconds

None **12/20/2018 9:38:56 AM** **Accession ID:** B6

Client:
Patient: **B6**

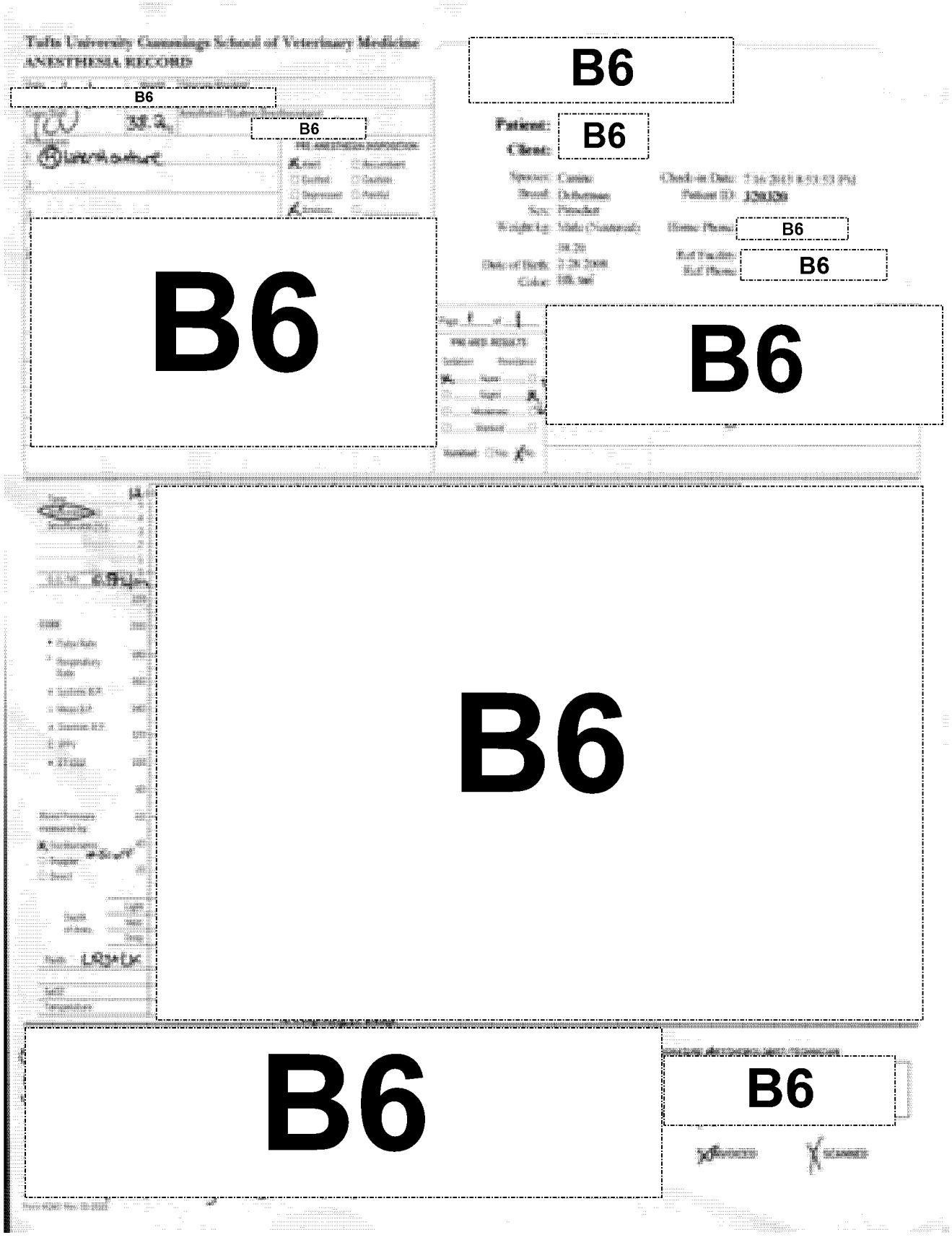
Test	Results	Reference Range	Units
TS (FHSA)		0 - 0	g/dL
AZO (FHSA)		0 - 0	
BG (FHSA)	**B6**	0 - 0	g/dL
TS (FHSA)		0 - 0	g/dL
PCV *		0 - 0	%

10/406 **B6**

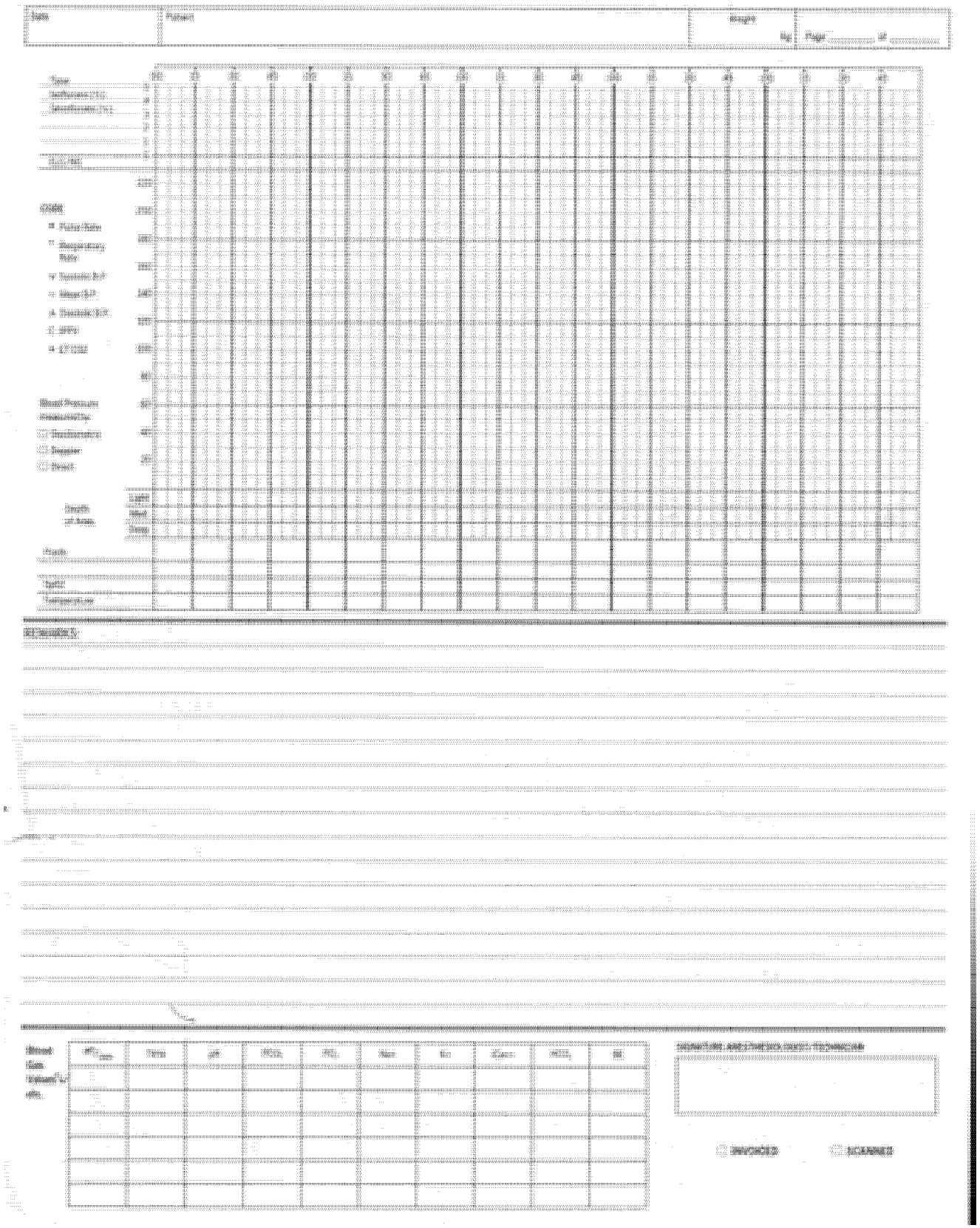
stringsoft

Printed Thursday, December 27, 2018

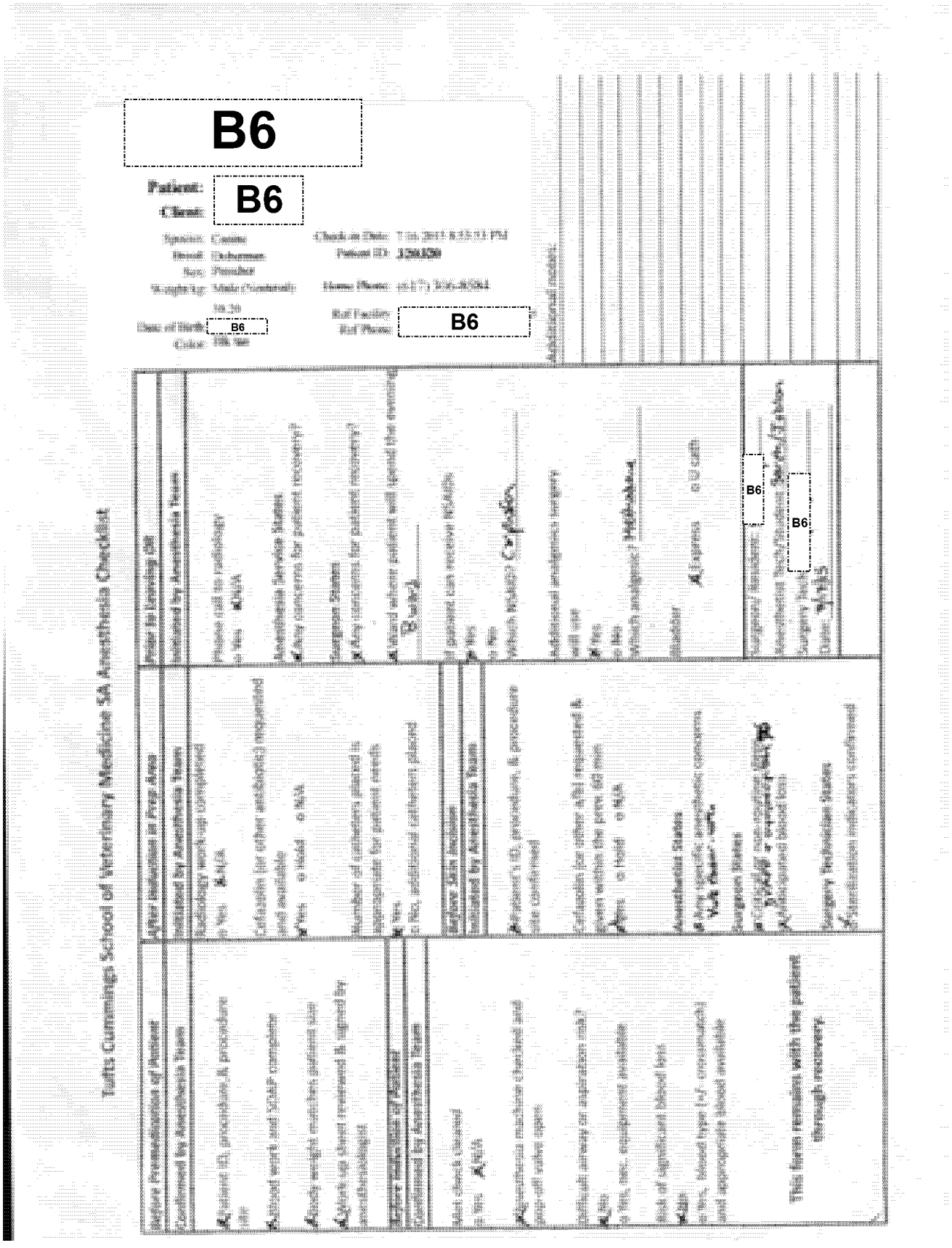
Anesthesia Record& checklist



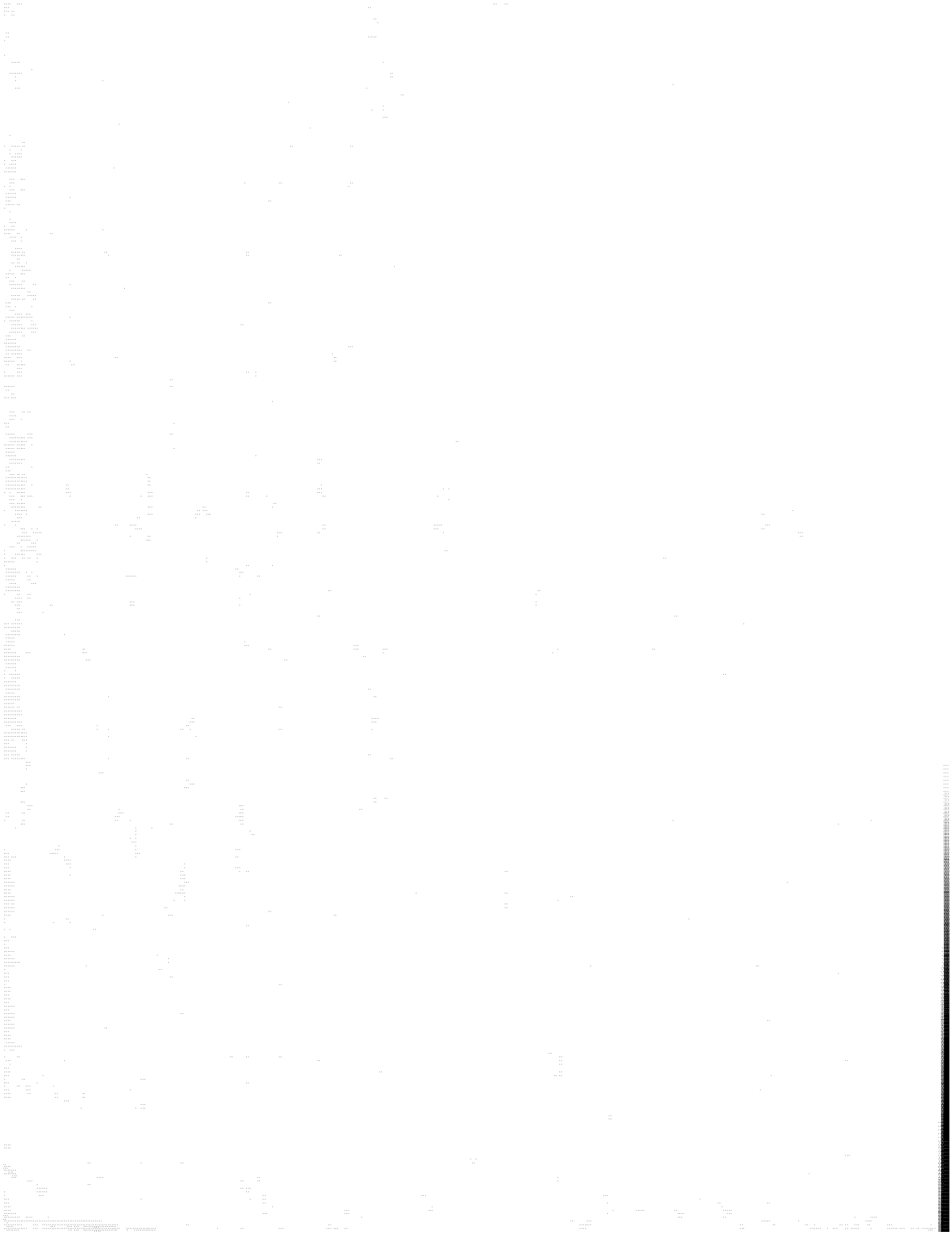
Anesthesia Record& checklist



Anesthesia Record& checklist



Anesthesia Record& checklist



transfusion request and monitoring form 7.17.2015

[redacted]

B6

POST-TRANSFUSION (1-2hr) PCV/TS (color of serum) : _____/_____ PT/PTT: _____/_____

Blue copy: Patient Record Yellow Copy: Blood Bank Pink Copy: Accounting

Client: B6
Patient: [illegible]

B6 insurance form

10/15/2015 9:59:01 PM From: B6 (Fax)

B4

VETERINARY RECORDS REQUEST

DATE: 10/15/2015

ATTENTION VETERINARIAN and/or STAFF: B6

B6

PET OWNER: B6 PET NAME: B6

POLICY NUMBER: B6 CLAIM NUMBER: B6

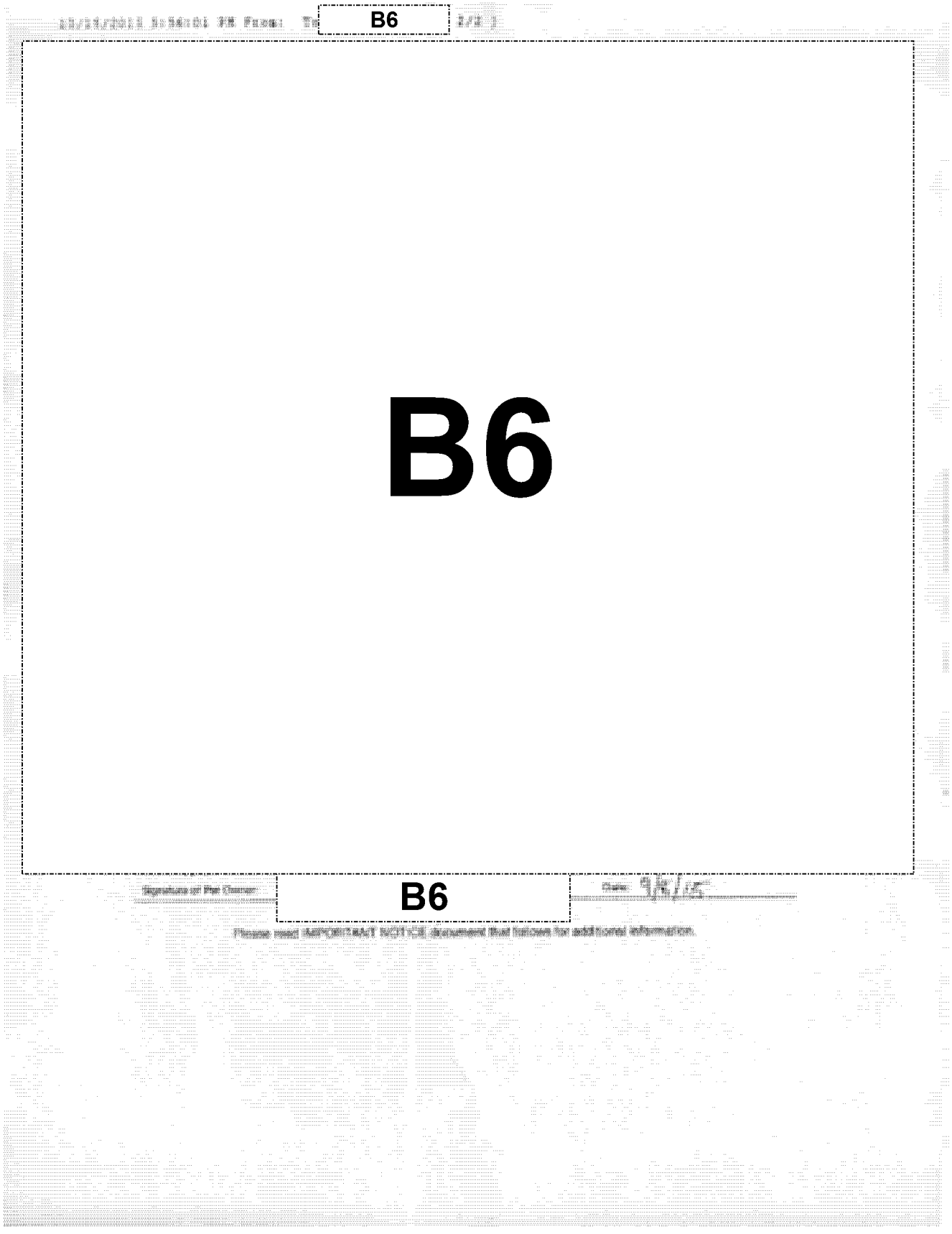
INFORMATION NEEDED:

1. MEDICAL RECORDS, INCLUDING DOCTOR'S NOTES AND LAB RESULTS FROM 6/1/2014 to Present

B6

Client: B6
Patient:

B6 insurance form



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Patient History

06/24/2015 11:43 AM	Appointment
07/08/2015 01:11 PM	Purchase
07/08/2015 01:13 PM	UserForm
07/08/2015 02:32 PM	UserForm
07/08/2015 02:32 PM	UserForm
07/08/2015 04:00 PM	Vitals
07/08/2015 04:00 PM	Vitals
07/08/2015 04:00 PM	Vitals
07/08/2015 04:00 PM	Vitals
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07/08/2015 04:30 PM	Purchase
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07/08/2015 04:33 PM	Vitals
07/08/2015 04:34 PM	Treatment
07/08/2015 04:56 PM	Purchase
07/08/2015 05:02 PM	Appointment
07/16/2015 08:55 PM	UserForm
07/16/2015 09:11 PM	Purchase
07/16/2015 09:11 PM	Purchase
07/16/2015 09:11 PM	Vitals
07/16/2015 09:18 PM	Vitals
07/16/2015 09:22 PM	Vitals
07/16/2015 09:38 PM	Treatment
07/16/2015 09:38 PM	Vitals
07/16/2015 09:39 PM	Treatment
07/16/2015 09:39 PM	Vitals
07/16/2015 09:43 PM	Treatment
07/16/2015 09:43 PM	Vitals
07/16/2015 10:03 PM	Treatment
07/16/2015 11:54 PM	Treatment
07/16/2015 11:59 PM	Treatment
07/16/2015 11:59 PM	Vitals
07/16/2015 11:59 PM	Treatment
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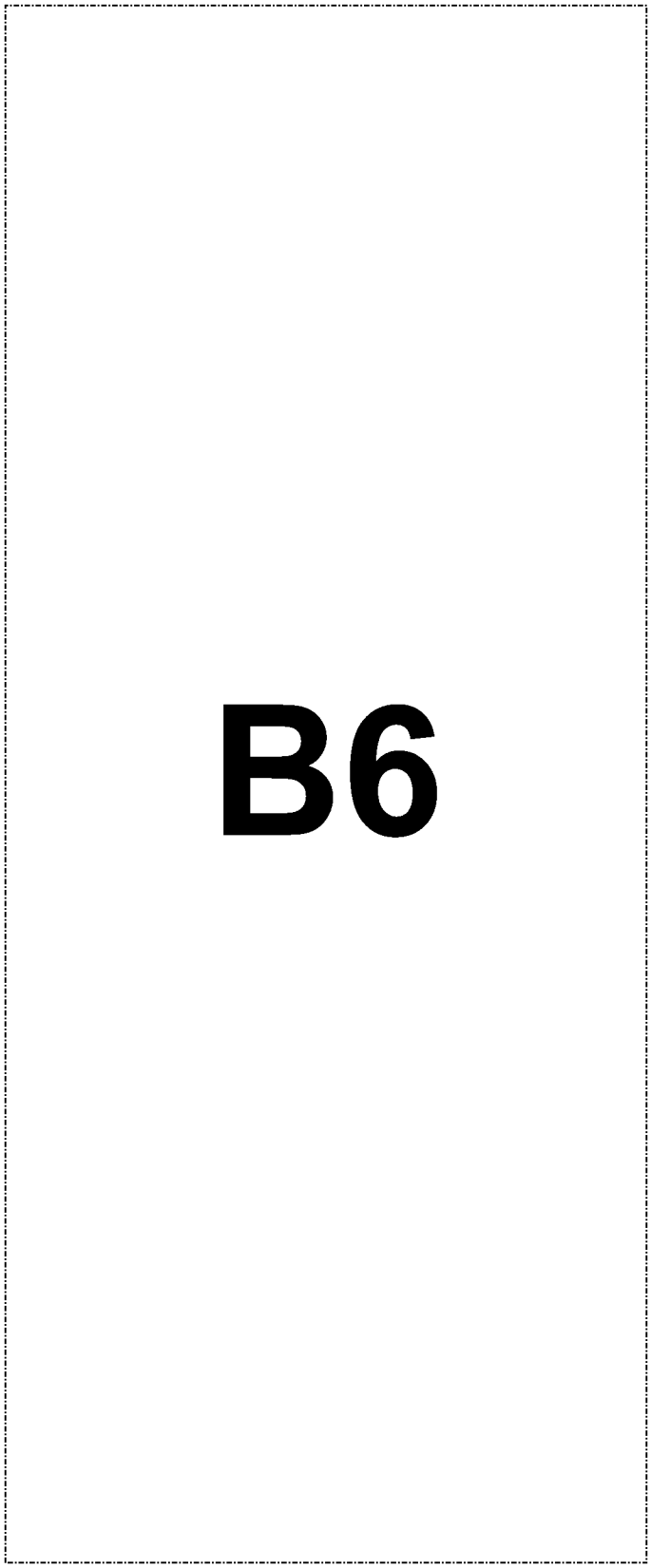

Client: B6
Patient:

Patient History

07/16/2015 11:59 PM	Vitals
07/17/2015 03:50 AM	Treatment
07/17/2015 03:50 AM	Vitals
07/17/2015 03:51 AM	Treatment
07/17/2015 03:51 AM	Treatment
07/17/2015 03:51 AM	Vitals
07/17/2015 03:51 AM	Treatment
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07/17/2015 03:51 AM	Treatment
07/17/2015 03:51 AM	Vitals
07/17/2015 07:15 AM	Vitals
07/17/2015 07:21 AM	Treatment
07/17/2015 07:21 AM	Vitals
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07/17/2015 09:11 AM	Treatment
07/17/2015 10:52 AM	Purchase
07/17/2015 10:53 AM	Treatment
07/17/2015 10:54 AM	Treatment
07/17/2015 11:10 AM	Prescription
07/17/2015 11:19 AM	UserForm
07/17/2015 11:27 AM	Treatment
07/17/2015 11:27 AM	Vitals
07/17/2015 11:51 AM	Vitals
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07/17/2015 02:46 PM	Vitals
07/17/2015 03:15 PM	Treatment
07/17/2015 03:15 PM	Vitals

B6

Patient History

07/17/2015 03:16 PM	Treatment
07/17/2015 03:16 PM	Vitals
07/17/2015 03:16 PM	Treatment
07/17/2015 03:16 PM	Vitals
07/17/2015 03:17 PM	Treatment
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07/17/2015 03:22 PM	Purchase
07/17/2015 03:22 PM	Purchase
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07/17/2015 09:13 PM	Purchase
07/17/2015 11:26 PM	Treatment
07/17/2015 11:26 PM	Vitals
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07/17/2015 11:26 PM	Treatment
07/17/2015 11:26 PM	Vitals
07/18/2015 03:02 AM	Treatment
07/18/2015 03:25 AM	Treatment
07/18/2015 03:25 AM	Treatment
07/18/2015 03:25 AM	Vitals
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07/18/2015 03:30 AM	Treatment
07/18/2015 03:30 AM	Vitals
07/18/2015 07:25 AM	Vitals
07/18/2015 07:26 AM	Treatment
07/18/2015 07:26 AM	Vitals
07/18/2015 07:40 AM	Vitals

B6

Patient History

07/18/2015 07:40 AM	Vitals
07/18/2015 08:00 AM	Treatment
07/18/2015 08:08 AM	Treatment
07/18/2015 08:08 AM	Treatment
07/18/2015 08:08 AM	Vitals
07/18/2015 08:08 AM	Treatment
07/18/2015 08:08 AM	Treatment
07/18/2015 08:08 AM	Vitals
07/18/2015 08:08 AM	Treatment
07/18/2015 08:08 AM	Vitals
07/18/2015 09:11 AM	Purchase
07/18/2015 10:03 AM	Prescription
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07/18/2015 11:41 AM	Treatment
07/18/2015 11:41 AM	Vitals
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07/18/2015 12:20 PM	Treatment
07/18/2015 12:20 PM	Vitals
07/18/2015 02:21 PM	Treatment
07/18/2015 03:05 PM	Treatment
07/18/2015 03:05 PM	Treatment
07/18/2015 03:05 PM	Vitals
07/18/2015 03:29 PM	Treatment
07/18/2015 03:30 PM	Treatment
07/18/2015 03:30 PM	Vitals
07/18/2015 03:30 PM	Treatment
07/18/2015 03:30 PM	Vitals

B6

Patient History

07/18/2015 07:21 PM	Treatment
07/18/2015 07:21 PM	Treatment
07/18/2015 07:21 PM	Vitals
07/18/2015 07:38 PM	Treatment
07/18/2015 07:38 PM	Vitals
07/18/2015 07:42 PM	Treatment
07/18/2015 07:48 PM	Treatment
07/18/2015 07:48 PM	Vitals
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07/18/2015 09:13 PM	Purchase
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07/18/2015 10:35 PM	Vitals
07/19/2015 12:01 AM	Treatment
07/19/2015 12:01 AM	Treatment
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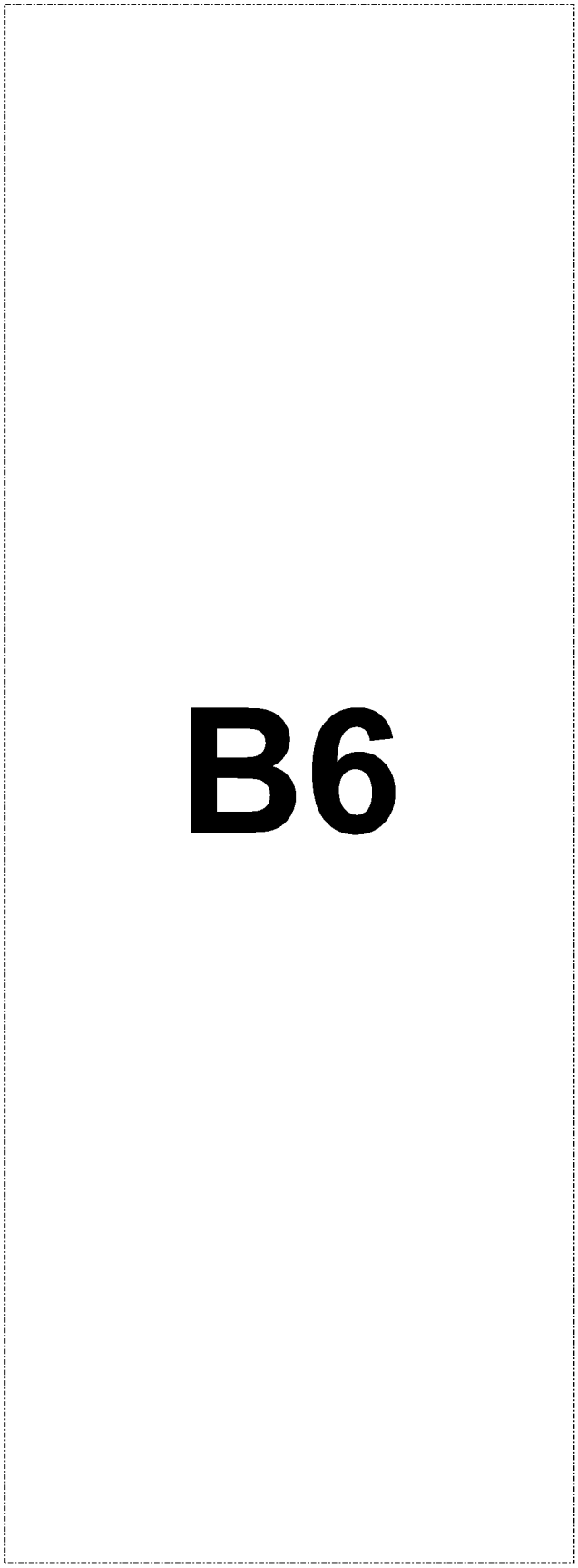
07/19/2015 04:30 AM	Treatment
07/19/2015 04:34 AM	Treatment



Client:
Patient: B6

Patient History

07/19/2015 04:34 AM	Vitals
07/19/2015 04:34 AM	Vitals
07/19/2015 04:40 AM	Treatment
07/19/2015 04:40 AM	Treatment
07/19/2015 04:40 AM	Vitals
07/19/2015 04:40 AM	Treatment
07/19/2015 04:40 AM	Vitals
07/19/2015 07:28 AM	Treatment
07/19/2015 07:28 AM	Vitals
07/19/2015 07:28 AM	Treatment
07/19/2015 07:28 AM	Treatment
07/19/2015 07:30 AM	Vitals
07/19/2015 07:35 AM	Treatment
07/19/2015 07:35 AM	Vitals
07/19/2015 07:35 AM	Treatment
07/19/2015 07:35 AM	Vitals
07/19/2015 07:35 AM	Treatment
07/19/2015 07:35 AM	Vitals
07/19/2015 08:20 AM	Treatment
07/19/2015 09:09 AM	Prescription
07/19/2015 09:09 AM	Prescription
07/19/2015 09:11 AM	Purchase
07/19/2015 09:29 AM	Deleted Reason
07/19/2015 09:29 AM	Deleted Reason
09/22/2015 02:48 PM	Appointment
10/07/2015 03:32 PM	UserForm
10/07/2015 03:32 PM	Purchase
11/15/2018 02:09 PM	Appointment
12/03/2018 10:44 AM	Appointment
12/03/2018 10:47 AM	Appointment
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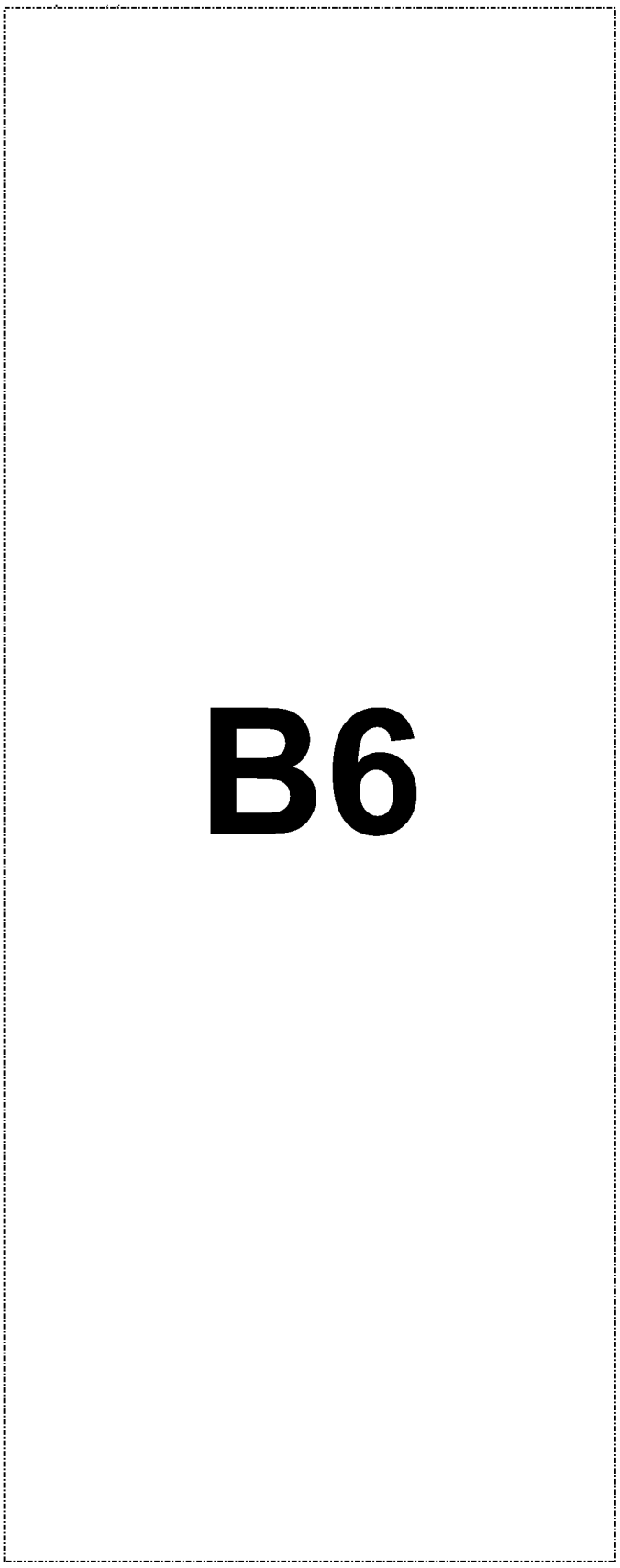

Patient History

12/04/2018 01:53 PM	Appointment
12/05/2018 09:13 AM	UserForm
12/05/2018 09:32 AM	Treatment
12/05/2018 09:35 AM	Vitals
12/05/2018 10:24 AM	Purchase
12/05/2018 10:24 AM	Purchase
12/05/2018 10:24 AM	Purchase
12/05/2018 10:56 AM	UserForm
12/05/2018 11:39 AM	Purchase
12/05/2018 11:40 AM	Prescription
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12/10/2018 01:51 PM	Purchase
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12/10/2018 01:57 PM	Prescription
12/10/2018 02:05 PM	Purchase
12/10/2018 02:29 PM	UserForm
12/13/2018 09:28 AM	Email
12/14/2018 10:43 AM	Appointment
12/19/2018 07:50 AM	Appointment
12/19/2018 07:52 AM	Appointment
12/20/2018 07:56 AM	UserForm
12/20/2018 08:06 AM	Vitals
12/20/2018 08:06 AM	Vitals
12/20/2018 09:07 AM	Vitals
12/20/2018 09:22 AM	Purchase
12/20/2018 09:28 AM	Vitals
12/20/2018 09:28 AM	Vitals
12/20/2018 09:28 AM	Vitals
12/20/2018 09:28 AM	Vitals
12/20/2018 09:28 AM	Vitals
12/20/2018 09:37 AM	Treatment

B6

Patient History

12/20/2018 09:39 AM	Labwork
12/20/2018 09:40 AM	Prescription
12/20/2018 09:48 AM	Purchase
12/20/2018 11:31 AM	Treatment
12/20/2018 11:31 AM	Treatment
12/20/2018 11:31 AM	Vitals
12/20/2018 11:31 AM	Treatment
12/20/2018 11:31 AM	Vitals
12/20/2018 11:32 AM	Treatment
12/20/2018 11:32 AM	Vitals
12/20/2018 12:45 PM	Prescription
12/20/2018 12:56 PM	Vitals
12/20/2018 01:14 PM	Purchase
12/20/2018 01:15 PM	Purchase
12/20/2018 01:22 PM	Prescription
12/20/2018 01:22 PM	Treatment
12/20/2018 01:22 PM	Vitals
12/20/2018 01:22 PM	Prescription
12/20/2018 01:23 PM	Treatment
12/20/2018 01:23 PM	Vitals
12/20/2018 01:24 PM	Prescription
12/20/2018 01:31 PM	UserForm
12/20/2018 01:45 PM	Purchase
12/20/2018 01:45 PM	Purchase
12/20/2018 01:45 PM	Purchase
12/20/2018 01:45 PM	Purchase
12/20/2018 01:45 PM	Purchase
12/20/2018 01:45 PM	Purchase
12/20/2018 01:53 PM	Treatment
12/20/2018 01:53 PM	Treatment
12/20/2018 01:59 PM	Purchase
12/20/2018 02:18 PM	UserForm
12/20/2018 02:50 PM	Purchase
12/20/2018 02:50 PM	Deleted Reason
12/20/2018 02:50 PM	Deleted Reason
12/20/2018 03:29 PM	Treatment
12/20/2018 03:29 PM	Vitals
12/20/2018 03:29 PM	Vitals
12/20/2018 03:36 PM	Treatment
12/20/2018 03:36 PM	Vitals
12/20/2018 03:37 PM	Treatment
12/20/2018 03:37 PM	Vitals
12/20/2018 03:38 PM	Treatment

B6

Client: B6
Patient:

Patient History

12/20/2018 03:38 PM	Vitals
12/21/2018 08:04 AM	Purchase

B6

B6

B6

B6

B6

B6

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B6

STANDARD CONSENT FORM

I am the owner, or agent for the owner, of the above described animal and have the authority to execute consent. I hereby authorize the Cummings School of Veterinary Medicine at Tufts University (herein after Cummings School) to prescribe for treatment of said animal according to the following terms and conditions.

Cummings School and its officers, agents and employees will provide such veterinary medical care as they deem reasonable and appropriate under the circumstances.

Cummings School and its officers, agents, and employees will use all reasonable care in the treatment of the above mentioned animal, but will not be liable for any loss or accident that may occur or any disease that may develop as a result of the care and treatment provided.

I understand that the above identified animal may be treated by Cummings School students under the supervision and assistance of Cummings School staff members.

In executing this form, I hereby expressly acknowledge that risks, benefits and alternative forms of treatment have been explained to me. I understand said explanation, and I consent to treatment. Should any additional treatments or diagnostics be required during the continued care of my animal, I understand that I will be given the opportunity to discuss and consent to these additional procedures. I understand that further or additional treatment may be required without an opportunity for discussion and consideration by me, in the case of the development of any life-threatening emergency during the continued care of my animal and I expressly consent to all such reasonable treatment as required. I realize and understand that results cannot be guaranteed.

If any equipment is left with the animal, it will be accepted with the understanding that Cummings School assumes no responsibility for any loss of equipment that may occur.

I agree to pick up the animal when notified that it is ready for release.

In the event the animal is not picked up, and ten (10) days have expired since a registered letter was sent to the address given above, notifying me to call for the animal, the animal may be sold or otherwise disposed of in a humane manner and the proceeds applied to the charges incurred in caring and treating the animal. Failure to remove said animal will not and does not relieve me from obligation for the costs of services rendered.

I hereby grant to the Cummings School of Veterinary Medicine at Tufts University, its officers and employees (collectively referred to herein as Cummings School), and its agents and assigns (the Grantees) the irrevocable rights to photograph / videotape the operation or procedure to be performed, including appropriate and otherwise use such photographs and images for, and in connection with, a Grantee's medical, scientific, educational, and publicity purposes, by any means, methods and media (print and electronic) now known or, in the future, developed that the Grantee deems appropriate (provided that such photographs and images may not be used in for-profit commercials, unless such commercials are publicizing educational programs at Cummings School). As medical and

surgical treatment necessitates the removal of tissue, cells, fluids or body parts of my animal, I authorize the Caretakers to dispose of or use these tissues, cells, fluids or body parts for scientific and educational purposes.

I understand that a FINANCE CHARGE will be applied to all accounts unpaid after 30 days. The FINANCE CHARGE is computed on a monthly rate of 1.33% per month, which is an annual percentage rate of 16% applied to the average daily balance outstanding, with a minimum fee of $.50.

I do further agree that should any payment, or the full amount of the sum stated above, become overdue more than 30 days from the above-agreed upon time of payment or payments, the entire balance shall be considered in default and become due and payable. I further agree to be responsible for any or all collection agency and/or attorney fees necessary to collect the full amount.

I do further agree to comply with hours of visitation in conjunction with our Hospital's policy.

I have read, understand, and agree to accept the terms and conditions herein.

Owner's name: B6 Date: 7/8/2015

Owner's address: B6

B6

Owner Date 7/8/15

If the individual admitting the animal is someone other than the legal owner, please complete the portion below:

The owner of the animal B6 has granted me authority to obtain medical treatment, and to bind this owner to pay the veterinary medical services provided at Cummings School pursuant to the terms and conditions described above.

Authorized Agent – Please Print

Agent's Signature

Street Address

Date

Town/City State Zip

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Foster Hospital for Small Animals
56 Willard Street
North Grafton, MA 01536
Telephone: (508) 839-5395
Fax (508) 839-8739
http://www.tufts.edu/vet/

Surgery Liaison: 508-887-4794

Patient Name: B6
Signalement: B6 Years Old Blk/tan Male (Neutered) Doberman Pinscher

Owner Name:
Address: B6

Patient ID: 326020

Contact Clinician/ Student: B6

Discharge Instructions

Admit Date: B6 1:11:52 PM
Discharge Date:

Diagnosis: 1. B6

Procedures:
1. Pysical Exam
2. VD pelvic X-rays of right knee

Medications:

Dispense:

Continue:

Diet: Please continue Brent's regular diet.

B6

B6

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Fax: (508) 839-8739
http://www.tufts.edu/vet/

Radiology Request & Report

Patient
Name: B6
Species: Canine
Bik/tan Male (Neutered)
Doberman Pinscher
Birthdate: B6

Owner
Name: B6
Address: B6

Patient ID: 328320
Date of request: B6

Attending Clinician: B6 DVM, DACVS Student: B6

Date of exam: B6

Patient Location: Ward/Cage: Weight (kg) 37.3

- ☐ Inpatient
- ☑ Outpatient Time:
- ☐ Waiting
- ☐ Emergency

Sedation
- ☐ IMG
- ☐ OIMG
- ☐ 1/2 dose OIMG
- ☑ DexDomitor/Butorphanol
- ☐ Anesthesia to sedate/anesthetize

Examination Desired: B6

Presenting Complaint:
New cruciate evaluation, possibly sx at rDVM

B6

Conclusions:

B6

Radiologists:

Primary: B6 DVM

Reviewing: B6 , DACVR

B6 , DVSc, DACVR

Dates

Reported: 7.9.2015

Finalized: 7.10.2015

Tufts

Foster Hospital for Small Animals

Treatment Plan

B6

B6

B6

B6

B6

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B6

B6 Male (Neutered)
Canine Doberman Pincher
Patient ID: 328328

SURGERY REPORT

Date of report: B6 Attending Clinician: B6

Date of procedure: B6

Primary Surgeon: B6

Student: B6

Procedure(s) performed: B6

B6

Concerns:

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http://www.tufts.edu/vet/

Surgery Liaison: 508-887-4794

Patient
Name: B6
Signalement: B6 Years Old Silky/Toy Male (Neutered) Doberman Pinscher

Owner
Name:
Address: B6

Patient ID: 326328

Contact Clinician:
Alternate Clinician:
Student: B6

Discharge Instructions

Admit Date:
Discharge Date: B6

Diagnosis: 1 B6

Procedures: 1

Medications:
Dispense: B6

Diet:

CASE SUMMARY
General summary:
B6

B6

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Fax (508) 839-8739
http://vetmed.tufts.edu/

Patient Name: B6
Signalement: B6 Years Old Blk/Tan Male (Neutered) Doberman Pinscher

Patient ID: 328320

Contact Clinician: B6 MM, DACVS
Alternate Clinician:
Student:

Owner Name:
Address: B6

RE-EXAMINATION FORM

Date: 10/7/2015
Problem: Chief Recheck No Xrays

History:

B6

B6

B6

B6

B6

B6

B6

B6

B6

Cummings
Veterinary Medical Center
AT TUFTS UNIVERSITY
Cardiology Liaison: 508-887-4096

B6

B6 ID: 320330
Canine
B6 Years Old Male (Neutered) Doberman
Pinscher
Black/Tan

Cardiology Appointment Report

Date: 12/5/2018

Attending Cardiologist:
John E. Rush DVM, MS, DACVIM (Cardiology), DACVECC

B6

Cardiology Resident:
B6

Cardiology Technician:
B6

Student: B6 , V'19

Presenting Complaint:
Evaluation of DCM/arrhythmia

Concurrent Diseases:
History of Anaplasma
History of vonWillebrand disease (40% as of 7/15)
History of skin allergies
History of elevated ALT

General Medical History:

B6

Diet and Supplements:
Home cooked diet consisting of lamb protein with broccoli, egg, brewer's yeast, cod liver oil, safflower oil TID

New 4 days ago:
Taurine 500 mg tablet PO BID
Coenzyme Q-10 supplement SID
L-carnitine BID
Coenzyme-10 supplement SID

Cardiovascular History:
Prior CHF diagnosis? No
Prior heart murmur? No
Prior ATE? No
Prior arrhythmia? Yes
Monitoring respiratory rate and effort at home? No
Cough? No
Shortness of breath or difficulty breathing? No, just not as apt to exercise, stops often during walks
Syncope or collapse? No
Sudden onset lameness? No, not outside of arthritis
Exercise intolerance? Yes

Current Medications Pertinent to CV System:

B6

Cardiac Physical Examination:

B6

Muscle condition:
- ☑ Normal
- ☑ Mild muscle loss
- ☐ Moderate cachexia
- ☐ Marked cachexia

Cardiovascular Physical Exam:
Murmur Grade:
- ☑ None
- ☑ I/VI s/-
- ☐ II/VI
- ☐ III/VI
- ☐ IV/VI
- ☐ V/VI
- ☐ VI/VI

Murmur location/description: systolic left apical

Jugular vein:
- [x] Bottom 1/3 of the neck
- [ ] Middle 1/3 of the neck
- [ ] 1/2 way up the neck
- [ ] Top 2/3 of the neck

Arterial pulses:
- [ ] Weak
- [x] Fair
- [ ] Good
- [ ] Strong
- [ ] Bounding
- [ ] Pulse deficits
- [ ] Pulsus paradoxus
- [ ] Other:

Arrhythmia:
- [ ] None
- [ ] Sinus arrhythmia
- [x] Premature beats
- [ ] Bradycardia
- [ ] Tachycardia

Gallop:
- [ ] Yes
- [x] No
- [ ] Intermittent
- [ ] Pronounced
- [ ] Other:

Pulmonary assessments:
- [ ] Eupneic
- [ ] Mild dyspnea
- [ ] Marked dyspnea
- [x] Normal BV sounds
- [ ] Pulmonary crackles
- [ ] Wheezes
- [ ] Upper airway stridor

Abdominal exam:
- [x] Normal
- [ ] Hepatomegaly
- [ ] Abdominal distension
- [ ] Mild ascites
- [ ] Marked ascites

Problems:
Diagnosed DCM and ventricular arrhythmia

Diagnostic plan:
- [x] Echocardiogram
- [ ] Chemistry profile
- [x] ECG
- [x] Renal profile
- [x] Blood pressure
- [ ] Dialysis profile
- [ ] Thoracic radiographs
- [ ] NT-proBNP
- [ ] Troponin I
- [ ] Other tests:

Echocardiogram Findings:
General/2-D findings:

B6

Doppler findings:
Trace MR, Trace TR

Mitral inflow:

☐ Summated
☑ Normal
☐ Delayed relaxation
☐ Pseudonormal
☐ Restrictive

ECG findings:
NSR with frequent VPCs and APCs

Radiographic findings:

B6

Assessment and recommendations:

B6

Final Diagnosis:
DCM
Ventricular and supraventricular ectopy

Heart Failure Classification Score:
ISACHC Classification:
☐ Ia
☑ Ib
☐ II
☐ IIIa
☐ IIIb

ACVIM Classification:
☐ A
☐ B1
☑ B2
☑ C
☐ D

M-Mode:

IVSd	B6	cm
LVIDd		cm
LVPWd		cm
IVSs		cm
LVIDs		cm
LVPWs		cm
EDV(Teich)		ml
ESV(Teich)		ml
EF(Teich)		%
%FS		%
SV(Teich)		ml
Ao Diam		cm
LA Diam		cm
LA/Ao		
EPSS		cm
Max LA		cm
TAPSE		cm

M-Mode Normalized

IVSdN	B6	(0.290 - 0.520)
LVIDdN		(1.350 - 1.730) !
LVPWdN		(0.330 - 0.530)
IVSsN		(0.430 - 0.710) !
LVIDsN		(0.790 - 1.140) !
LVPWsN		(0.530 - 0.780) !

2D

Ao Diam	B6	cm
IVSd		cm
LVIDd		cm
LVPWd		cm
EDV(Teich)		ml
IVSs		cm
LVIDs		cm
LVPWs		cm
ESV(Teich)		ml
EF(Teich)		%
%FS		%
SV(Teich)		ml
LVLd LAX		cm
LVAd LAX		cm
LVEDV A-L LAX		ml
LVEDV MOD LAX		ml
LVLs LAX		cm
LVAs LAX		cm
LVESV A-L LAX		ml
LVESV MOD LAX		ml
HR		BPM

EF A-L LAX		%
LVEF MOD LAX		%
SV A-L LAX		ml
SV MOD LAX		ml
CO A-L LAX		l/min
CO MOD LAX		l/min
LV Length		cm
SA IA		cm
SA IA / Ao Diam		
LV Diameter		cm
Doppler		
MV E Vel		m/s
MV Decl		ms
MV A Vel		m/s
MV E/A Ratio		
E'		m/s
E/E'		
MR Vmax		m/s
MR maxPG		mmHg
AV Vmax		m/s
AV maxPG		mmHg
PV Vmax		m/s
PV maxPG		mmHg

B6

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Treatment Plan

B6

B6

B6

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Fax (508) 839-7951
http://vetmed.tufts.edu/

B6

B6 Male (Neutered)
Canine Doberman Pinscher Black/Tan
320320

Biopsy Request

Doctor to serve as contact: B6
(if primary contact is not available during business hours, provide a secondary contact, as well)
Phone/pager:
Email: B6

Total # of anatomic sites sampled (each site will be charged separately): 1

Total # of separate containers submitted: 2

Images sent to pathpics@tufts.edu?
- ☐ Yes
- ☑ No

CASE SUMMARY (CONCISE DESCRIPTION of: time sequence, therapy, summary of abnormal clinical pathology and diagnostic imaging lesion size, margin labels/orientation if relevant):

B6

CLINICAL DIAGNOSES/DIFFERENTIALS:

CONTAINER 1. (In addition to site specific history include number of tissue pieces): caudal maxillary mass

CONTAINER 2. (In addition to site specific history include number of tissue pieces): margins of mass

CONTAINER 3. (In addition to site specific history include number of tissue pieces):

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Fax (508) 839-7953
http://vetmed.tufts.edu/

Patient Name: B6
Signalement: Years Old Black/Tan Male (Neutered) Doberman Pinscher

Owner Name: B6
Address:

Patient ID: 326020

Contact Clinician: B6 DVM, DACVS
Alternate Clinician: B6 DVM (SA Surgery Resident)
Student: B6 VET

Discharge Instructions

Admit Date: 12/20/2018
Discharge Date: 12/28/2018

B6

B6

Prescription Refill Disclaimer:
For the safety and well-being of our patients, your pet must have had an examination by one of our veterinarians within the past year in order to obtain prescription medications.

Ordering Food:
Please check with your primary veterinarian to purchase the recommended diet(s). If you wish to purchase your food from us, please call 7-10 days in advance (XXX-XXX-4624) to ensure the food is in stock. Alternatively, veterinary diets can be ordered from online retailers with a prescription/veterinary approval.

Clinical Trials:
Clinical trials are studies in which our veterinary doctors work with you and your pet to investigate a specific disease process or a promising new test or treatment. Please see our website: url.tufts.edu/vmg/clinical-studies

B6

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http://www.tufts.edu/vet/

B6

B6 Male (Neutered)
Canine: Doberman Pinscher Blk/tan
3203320

7/8/2015

Hi B6

B6

If you have any questions, or concerns, please contact us at 508-887-4888.

Thank you,

B6 DVM, DACVS

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http://www.tufts.edu/vet/

B6

B6

B6 Male (Neutered)
Canine: Doberman Pinscher Blk/tan
3203320

7/21/2015

Dear Dr. B6

Thank you for referring B6 with their pe B6

Please see the attached discharge instructions.

If you have any questions, or concerns, please contact us at 508-887-4988.

Thank you,

B6 DVM, DACVS

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B6

B6

Male (Neutered)
Canine: Doberman Pinscher: Blk/tan
3703320

10//2015

Hi B6

Thank you for referring B6 with their pet B6
See attached owner instructions. Brem is doing well, although he has had a few episodes of trauma in the recovery period.

B6

If you have any questions, or concerns, please contact us at 508-887-4888.

Thank you,

B6 DVM, DACVS

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B6

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http://vetmed.tufts.edu/

B6

Male (Neutered)
Canine Doberman Pincher
Black/Tan
320330

12/5/2018

Dear Dr. B6

Thank you for referring B6 with their pet B6

If you have any questions, or concerns, please contact us at 508-887-4988.

Thank you,

B6 DVM (Cardiology)

From: Freeman, Lisa <Lisa.Freeman@tufts.edu>
To: Reimschuessel, Renate
CC: Jones, Jennifer L
Sent: 7/20/2018 12:06:11 PM
Subject: RE: 800.267-FDA Case Investigation for B6 (EON-358523)

Dear Renata and Jennifer
That seems reasonable. I was never contacted about the other cases that I submitted. There was some confusion about the way I submitted them so I want to be sure you actually got them B6 B6 I'm sure you're all getting slammed with reports (and there will probably be even more coming now) but just wanted to check to be sure they got recorded.
Thanks
Lisa

From: Reimschuessel, Renate [mailto:Renate.Reimschuessel@fda.hhs.gov]
Sent: Friday, July 20, 2018 7:55 AM
To: Freeman, Lisa <Lisa.Freeman@tufts.edu>
Cc: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Subject: RE: 800.267-FDA Case Investigation for B6 (EON-358523)

Dear Lisa
Thanks for gathering the information.
I think, since we are getting so many reports since our CVM update, we should pass on the B6 case as it is not clear-cut.

I think Jen is more familiar with the B6 case, so I'll let her respond regarding that one.
Thank you again for all your work on this investigation.
rr

Renate Reimschuessel V.M.D. Ph.D. Director Vet-LIRN
Phone 1- 240-402-5404
Fax 301-210-4685
http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm

From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Thursday, July 19, 2018 5:59 PM
To: Reimschuessel, Renate <Renate.Reimschuessel@fda.hhs.gov>
Subject: RE: 800.267-FDA Case Investigation for B6 (EON-358523)

Dear Renate
In looking back through this case, I'm not sure this is a completely clear-cut one. The dog has degenerative mitral valve disease and CHF but also has reduced cardiac contractility so might be a combination.
Do you still want me to collect the info below?

Also, I have an update on B6 who died at home last week. I do have food from the owner if you want that.
Thanks
Lisa

Lisa M. Freeman, DVM, PhD, DACVN
Professor

Cummings School of Veterinary Medicine
Friedman School of Nutrition Science and Policy
Tufts Clinical and Translational Science Institute
Tufts University
www.petfoodology.org

From: Reimschuessel, Renate <Renate.Reimschuessel@fda.hhs.gov>
Sent: Tuesday, July 17, 2018 11:48 AM
To: Freeman, Lisa <lisa.freeman@tufts.edu>
Subject: 800.267-FDA Case Investigation for B6 (EON-358523)

Dear Dr. Freeman,
Thank you for submitting your consumer complaint to FDA. I'm sorry to hear about B6 illness.
As part of our investigation, we'd like to request:

- **Full Medical Records**
  - Please email (preferred) or fax (301-210-4685) a copy of B6 **entire** medical history (not just this event), including any referral diagnostics.
- **Phone interview** about B6 diet and environmental exposures
  - Please confirm permission to contact the owner.
  - The interview generally lasts 30 minutes.

I attached a copy of our Vet-LIRN network procedures. The procedures describe how Vet-LIRN operates and how veterinarians help with our case investigations.
Please respond to this email so that we can initiate our investigation.

Thank you kindly, especially for submitting multiple cases,
Dr. Reimschuessel

Renate Reimschuessel V.M.D. Ph.D.
Director: Vet-LIRN
(Veterinary Laboratory Investigation and Response Network)
Center For Veterinary Medicine, FDA,
8401 Muirkirk Road, Laurel, MD 20708
Phone 1-240-402-5404 Fax 301-210-4685
EMAIL: renate.reimschuessel@fda.hhs.gov

Vet-LIRN
http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm

Phish-Pharm
http://www.fda.gov/AnimalVeterinary/ScienceResearch/ToolsResources/Phish-Pharm/default.htm

Aquaculture
http://www.fda.gov/AnimalVeterinary/ScienceResearch/ResearchAreas/ucm130892.htm

From: Freeman, Lisa <Lisa.Freeman@tufts.edu>
To: Jones, Jennifer L
Sent: 8/3/2018 9:23:00 AM
Subject: RE: 800.267-FDA Case Investigation for B6 (EON-358523)
Attachments: B6 appt 5-25-18.pdf; B6 cardi appt 5-17-18.pdf; B6 client comm.pdf; B6 discharge 5-18-18.pdf; B6 discharge 5-25-18.pdf; B6 ecg 5-25-18.pdf; B6 profile and t4.pdf; B6 rads 5-18-18.pdf; B6 rdvm records and taurine.pdf; B6 soap.pdf

Hi Jen
I'm attaching records from B6 re: B6
She's also given permission for you to contact her.

B6

I still have food in my office from

B6

if you want any of that

Thanks
Lisa

Lisa M. Freeman, DVM, PhD, DACVN
Board Certified Veterinary Nutritionist™
Professor
Cummings School of Veterinary Medicine
Friedman School of Nutrition Science and Policy
Tufts Clinical and Translational Science Institute
Tufts University
www.petfoodology.org

From: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Sent: Friday, July 20, 2018 8:47 AM
To: Freeman, Lisa <lisa.freeman@tufts.edu>
Cc: Reimschuessel, Renate <Renate.Reimschuessel@fda.hhs.gov>
Subject: RE: 800.267-FDA Case Investigation for B6 (EON-358523)

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Tel: 240-402-5421

U.S. FOOD & DRUG ADMINISTRATION

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Phone 1- 240-402-5404
Fax 301-210-4685
http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm

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To: 'Freeman, Lisa'
Sent: 8/31/2018 1:03:03 PM
Subject: B6

Thank you, Lisa! Enjoy your weekend,
Jen

Jennifer Jones, DVM
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From: Freeman, Lisa <Lisa.Freeman@tufts.edu>
Sent: Wednesday, August 29, 2018 6:45 PM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>
Subject: B6

Dear Jen,
I just spoke to B6 owner. I already submitted his case and sent in his food earlier this week (he is deceased).
They gave permission to be contacted directly for more info. Their phone is B6
Thanks
Lisa

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To: Jones, Jennifer L
Sent: 8/22/2018 6:14:37 PM
Subject: RE: 800.267-FDA Case Investigation for B6 (EON-358523)
Attachments: cardio report 7-11-18.pdf; discharge 7-4-18.pdf; echo report 7-3-18.pdf; B6 bnp 7-3-18.pdf; B6 discharge 7-11-18.pdf; B6 profile 7-11-18.pdf; B6 7-3-18.pdf

Hi Jen
I think you're probably right. In addition to B6 we've noted a few that don't have clear-cut DCM but have reduced fractional shortening. I've recorded these and will try to recheck them
*Boxer with 3rd degree AV block but also cardiac enlargement (Earthborn diet)
*Border collieX with reduced contractile function (Merrick – I have a sample of his diet)
*Mix breed with a murmur on Zignature (no echo done)
*Catahoula with a PDA but reduced contractile function on Taste of the Wild
*German Shepherd with mitral valve disease with questionable contractile function (unknown diet)
*Boxer with reduced contractile function eating 4Health

I'm attaching B6 files. We have not heard from owners recently
Lisa

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Sent: Wednesday, August 22, 2018 12:46 PM
To: Freeman, Lisa <lisa.freeman@tufts.edu>
Subject: RE: 800.267-FDA Case Investigation for B6 (EON-358523)

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I'm curious if we may be seeing a spectrum of disease with these complaints. Can you forward B6 medical records please?
Thank you,
Jen

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To: 'Freeman, Lisa'
CC: Reimschuessel, Renate
Sent: 8/1/2018 6:52:47 PM
Subject: RE: 800.267-FDA Case Investigation for B6 (EON-358523)

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Subject: RE: 800.267-FDA Case Investigation for B6 (EON-358523)
Attachments: B6 dcm taurine deficiency 7 7 17.pdf; B6 august 2017 echo.prnx; B6 B6 medical records.prnx; B6 nutrition request.prnx; B6 diet history.prnx

Hi Jen
I'll ask B6 to send their records. I'm attaching what I have from B6 and the primary care vet plus some Tufts records including diet history.
I don't know if owner still has the original food but will check
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  - The interview generally lasts 30 minutes.

I attached a copy of our Vet-LIRN network procedures. The procedures describe how Vet-LIRN operates and how veterinarians help with our case investigations.
Please respond to this email so that we can initiate our investigation.

Thank you kindly, especially for submitting multiple cases,
Dr. Reimschuessel

Renate Reimschuessel V.M.D. Ph.D.
Director: Vet-LIRN
(Veterinary Laboratory Investigation and Response Network)
Center For Veterinary Medicine, FDA,
8401 Muirkirk Road, Laurel, MD 20708
Phone 1- 240-402-5404 Fax 301-210-4685
EMAIL : renate.reimschuessel@fda.hhs.gov

Vet-LIRN

http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm

Phish-Pharm

http://www.fda.gov/AnimalVeterinary/ScienceResearch/ToolsResources/Phish-Pharm/default.htm

Aquaculture

http://www.fda.gov/AnimalVeterinary/ScienceResearch/ResearchAreas/ucm130892.htm

rDVM B6 HX 6/16/16-6/24/17 B6 Echo 6/19/17)

B6

Patient ID#: 7040-5

Owner: B6
(Last name) (First name)

B6

Spouse/Other:
(Last name) (First name)

Address: B6
(Street) (City/town) (State) (Zip code)

Contact Info: Primary Ph # (B6) Other Ph# (_____) _____

Other Ph #(_____) _____ Email: B6

Pet: B6 Gender: M Spay/Neuter: B6 C.P. | SAH

Species: Canine Breed: boxer

DOB: B6 Color: brindle

Annual Exam				2/17						
DA2PP										
Lepto										
DA2PP 3-year										
Bordetella										
Lyme										
Rabies										
HWT										
SNAP 4DX										
Fecal										
Other										

B6

* Not Here

Significant History/Comments:

CAUTION: _____

2/16 bronchopneumonia B6

6/16 B6 Cardiology Cx (Yn nnnnn) * see report

1/17 Home Again 6/17 severe DCM – poss. 2° to Taurine Def.

985 112 008 500 045

rDVM B6 HX 6/16/16-6/24/17 B6 Echo 6/19/17)

B6

PAGE: 7

PATIENT NAME B6 B6 boxer M OWNER'S NAME B6

MEDICAL RECORD

MO.	DATE DAY	YR.	PROB. NO.	SOAP
6	16	16		
			wt	
6	24	16		
6	30	16		
7	19	16		

B6

rDVM B6 HX 6/16/16-6/24/17 B6 Echo 6/19/17)

B6

PAGE: 8

PATIENT NAME B6 | B6 boxer M | OWNER'S NAME B6

MEDICAL RECORD

MO.	DAY	YR.	PROB. NO.	SOAP
8	27	16		
10	12	16		
11	22	16		
		wt-	64.7	
11	29	16		

B6

rDVM B6 HX 6/16/16-6/24/17 B6 Echo 6/19/17)

B6

PAGE: 9

PATIENT NAME B6 B6 boxer M OWNER'S NAME B6

MEDICAL RECORD

MO.	DATE DAY	YR.	PROB. NO.	SOAP
1	5	17		
			wt	
1	7	17		
1	11	17		
1	~~13~~	~~17~~		
1	12	17		
			wt	
1	13	17		
			wt	

B6

rDVM B6 HX 6/16/16-6/24/1 B6 cho 6/19/17)

B6

PAGE: 10

PATIENT NAME B6 boxer cm OWNER'S NAME B6

MEDICAL RECORD

MO.	DATE DAY	YR.	PROB. NO.	SOAP
1	13	17	(illegible)	

985 112 008 500 04

B6

1	14	17		
1	17	17		

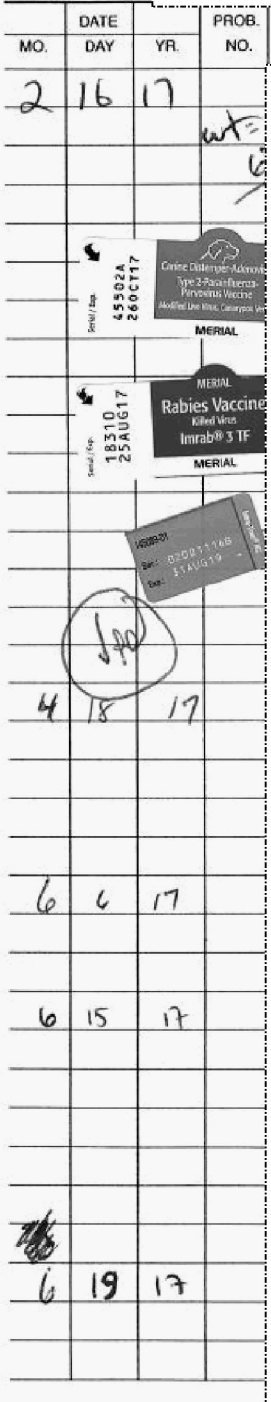
rDVM B6 HX 6/16/16-6/24/17 B6 Echo 6/19/17)

B6

PAGE: 11

PATIENT NAME B6 | boxer C M | OWNER'S NAME B6

MEDICAL RECORD



MO.	DAY	YR.	PROB. NO.	SOAP
2	16	17		wt= 6
4	18	17		
6	6	17		
6	15	17		
6	19	17		

B6

rDVM B6 HX 6/16/16-6/24/17 B6 Echo 6/19/17)

B6

PAGE: 12

PATIENT NAME B6 boxer CM OWNER'S NAME B6

MO.	DATE DAY	YR.	PROB. NO.	SOAP	MEDICAL RECORD
6	22	19			
6	24	19			
6	27	19			

B6

B6

B6

B6
Breed: Boxer
Sex: M
Color: brindle

B6

Visit Date: June 19, 2017

Dear Dr B6

I was pleased to see that B6 taurine level came back low, indicating there is a chance we can reverse the changes I saw on echo. I called and left a message for B6 and am copying below an email I sent her about his diet:

Hi B6
You probably already received my message with the news that B6 taurine level came back as low. This is good news because it means there is a chance the heart enlargement and weakened heart muscle appearance may be reversible. Even prior to receiving the bloodwork results I was consulting with a nutritionist who shared my concerns that he could have low taurine related to his diet. She expressed concern not just about the salmon based diet, but about the current diet as well based on the manufacturer/brand. So in addition to the taurine supplement, B6

B6

There are a lot of diet misconceptions and marketing information that makes diet selection very confusing for pet owners. I highly recommend the website set up by the Tufts veterinary school nutrition team at www.petfoodology.org. There are so many wonderful articles on there (I just spent a half hour surfing around because it is such wealth of great info!). I want to draw your

attention to the great article on the risks of raw diets (http://vetnutrition.tufts.edu/2016/01/raw-diets-a-healthy-choice-or-a-raw-deal/) and the one about the hype around grain-free diets (a pet peeve of mine) (http://vetnutrition.tufts.edu/2016/06/grain-free-diets-big-on-marketing-small-on-truth/). In short, since there is concern that B6 may have some food sensitivities, I encourage you to work with one of the nutritionists at either Tufts B6 to find a diet that will work for him, or at least that we switch him to a diet by a company who has done the research and due diligence to ensure a complete and balanced diet.

Meanwhile, you should continue the taurine and L-carnitine supplements, and the pimobendan as prescribed. It would be great to see B6 back sooner than the 3 month recheck however- to take a quick peek at his heart to see if (hopefully) things are changing for the better, and to recheck a taurine level. I think around 6 weeks from now makes sense, so let me know if you are interested in scheduling this, or if you have any questions.

Best,
Dr B6

Thank you for the referral and your continued support of B6 Please contact me if you need any more information regarding B6

Sincerely,

B6

B6

SOAP - Cardiology

Jun 19, 2017

B6

Patient:	B6	**DOB:**	B6
Species:	Canine	**Age:**	
Breed:	Boxer	**Sex:**	M
Color:	brindle	**Tag:**	
Doctor:	B6	**Weight:**	69.225 lbs. (31.4 kgs.)

Weight: 31.4 kgs.

Prior Medical History

As of 6/30/16
-Mildly elevated left and right ventricular outflow tract velocities: suspect normal variant +/- very mild aortic stenosis.
-Impression of mild left atrial enlargement: r/o age-related, other variant of undetermined cause

Presenting Complaint

Routine recheck

Current Medical History

General Complaints: O states that B6 has had 2 episodes since last visit, First episode was awhile ago (o not sure how long) in B6 He was running around with daughter and then acting totally out of it, staring at the ground, weak but did not lose consciousness- for around 30 min. Brought to ER in B6 but he was acting normal by the time they got there and they did not find any abnormalities on PE. Thursday am this happened when B6 was running with B6 in the back yard, and side swiped a bush, then stood up and seemed drunk/out of it (moving front legs in uncoordinated/crossing over fashion), lasted 5 min. then went back to normal. O did notice that on Thursday Gums were very pink during episode (not pale). No BM/urination/hypersalivation during episodes. Yesterday was doing " a ton" of reverse sneezing according to O. Great energy level otherwise. Does now have a good appetite, O has seen a kinesthesiologist due to low appetite B6 had been on strictly salmon based diet for past year, but they recommended changing/rotating protein sources (now beef and venison)- changed a few weeks ago and he is eating better.

Coughing?: No
Sneezing?: Yes
Vomiting: No
Polyuria: No
Polydipsia: No
Diarrhea?: No
Diet?: Was on Go Fresh limited ingredient salmon diet for about a year. A few weeks ago switched to Go Fresh venison and Fresh Now beef, with a raw patty at lunchtime (o unsure brand- something with two people's names)

Appetite: Normal
Any collapses or seizures?: Yes

Current Medications

Do you need any refills today?: No
First Cardiac Evaluation?: Yes
Referral Radiographs?: No

Physical Exam

B6

Echocardiogram

Two Dimensional Description: Given B6 history of panicked flailing on the echo table- we gave him B6 prior to echo. This provided ample/heavy sedation (next time could try without or give 1/2 that dose).

The left atrium is severely enlarged. The mitral valve appears normal. The left ventricular chamber is moderately dilated with mildly thin walls and severely globally depressed wall motion. The aortic root appears mildly small (breed variant) with normal aortic valve. The right atrium is moderately dilated. The tricuspid valve appears normal. The right ventricular chamber is mildly dilated. The pulmonary artery and pulmonic valve are normal.

B6

B6

ECHOCARDIOGRAPHIC DIAGNOSIS:

ECHOCARDIOGRAPHIC DIAGNOSIS:
-Dilated cardiomyopathy (severe), r/o idiopathic, secondary to taurine-deficiency, myocarditis, other
-Borderline pulmonary hypertension
-Mildly elevated left ventricular outflow tract velocity (dx 6/2016)

Comparison to previous studies:
There has been significant increase in left atrial size (from 3.86 cm on 2D one year ago), in left ventricular size (from 4.38 cm one year ago) and decrease in %FS (from 30.8% one year ago). MR and TR are new (suspect secondary to annular stretch). The right atrium and ventricle subjectively appear somewhat enlarged as well.

Electrocardiogram

Other Findings: ECG recording throughout the echo study showed normal sinus arrhythmia at 65-95 bpm (mostly ~70 bpm) with no ventricular ectopy recorded.

ELECTROCARDIOGRAPHIC DIAGNOSIS:
Normal sinus arrhythmia

Blood Pressure

Blood Pressure: 114/71 (84) mmHg (ave of 2 readings- very relaxed, snoozing with sedation on echo table)
Technique: petMAP
Cuff size: 5.5 cm
Site: Right front leg

Final Assessment

Final Diagnosis:
-Dilated cardiomyopathy (severe), r/o idiopathic, secondary to taurine-deficiency, myocarditis, other
-Borderline pulmonary hypertension
-Mildly elevated left ventricular outflow tract velocity (dx 6/2016)
-Normal sinus arrhythmia with no ventricular ectopy

Diagnostic Recommendations:

B6

Follow-Up:
Recheck 3 months with echocardiogram +/- thoracic radiographs (scheduled for September 11 at 9:30 am)

Consulting Cardiologist: B6 DVM; DACVIM (cardiology)

B6

Client Name:
Animal Name: B6
Client Phone:
MRN: 1373024
Species: Canine
Breed: Boxer
DOB: B6 Sex: M

Doctor:
Clinic: B6
Phone:
Fax:

Accession: B6
Collected: 6/19/2017
Received: 6/19/2017
Approval Date: 6/22/2017 9:16 AM

Taurine Level (plasma) Final Report

	Ref. Range/Males	6/19/2017 10:29 AM
SENDOUT		See attached link

Accession number: B6
This report continues... (Final)

B6

Client name: B6
MRN: 1373024

Accession: B6

B6

Report Print Date
Jun-22-2017 8:11:49 am

Owner:

B6

To:

Accession Number:
Reference Number:
Case Coordinator: B6

Received: 06/20/2017
Sampled:
Finalized: 06/22/2017

Phone:
Fax: B6

Final Report

TOXICOLOGY RESULTS

TAURINE

ANIMAL ID	B6
SPECIMEN ID	M17-19120-1-1
SPECIMEN DESC	PLASMA
TAURINE	47 nmol/mL

COMMENTS1
Canine taurine ranges: normal plasma 60-120 nmol/mL critical level <40 nmol/mL; whole blood normal 200-350 nmol/mL critical level <150 nmol/mL.

B6

Accession number: B6
END OF REPORT (Final)

B6

B6

Pet: B6
DOB
Breed: Boxer
Sex: M
Color: brindle

B6

Visit Date: June 19, 2017

Dear Dr. B6

Please see the accompanying cardiology report for our mutual patient, B6 was so sad to see tha B6 heart has changed quite a bit in the last year, and he now appears to have severe dilated cardiomyopathy. He had been on a limited ingredient salmon diet, only recently switched to beef and venison based diet, so I hold some hope that this may be a taurine deficiency manifestation (would be much better prognosis for him- so fingers crossed!). We have a taurine level pending, but of course this may not reflect historic deficiency due to his recent diet change. Meanwhile, I have prescribed B6 He has had two episodes of seeming woozy/disoriented and "out of it" after exertion, but they do not sound classic for arrhythmia-related (one episode lasted 30 minutes) and his ECG today was normal. We will continue to monitor for now (perhaps they were related to low output from systolic dysfunction and pimobendan will help). If they recur, we will check a 24 hour holter monitor (with B6 bad luck I wouldn't put it past him to also have a neurologic condition!). Thank you for the referral and your continued support of B6 Please contact me if you need any more information regarding B6

Sincerely,

B6

B6

B6

SOAP - Cardiology

Jun 19, 2017

B6

Patient: B6
Species: Canine
Breed: Boxer
Color: brindle
Doctor: B6

DOB: B6
Age: B6
Sex: M
Tag:
Weight: 69.225 lbs. (31.4 kgs.)

Weight: 31.4 kgs.

Prior Medical History

As of 6/30/16
-Mildly elevated left and right ventricular outflow tract velocities: suspect normal variant +/- very mild aortic stenosis.
-Impression of mild left atrial enlargement: r/o age-related, other variant of undetermined cause

Presenting Complaint

Routine recheck

Current Medical History

General Complaints: O states that B6 has had 2 episodes since last visit, First episode was awhile ago (o not sure how long) in B6 He was running around with daughter and then acting totally out of it, staring at the ground, weak but did not lose consciousness- lst around 30 min. Brought to ER in B6 but he was acting normal by the time they got there and they did not find any abnormalities on PE. Thursday am this happened when B6 was running with B6 in the back yard, and side swiped a bush, then stood up and seemed drunk/out of it (moving front legs in uncoordinated/crossing over fashion), lasted 5 min. then went back to normal. O did notice that on Thursday Gums were very pink during episode (not pale). No BM/urination/hypersalivation during episodes. Yesterday was doing " a ton" of reverse sneezing according to O. Great energy level otherwise. Does now have a good appetite, O has seen a kinesthesiologist due to low appetite B6 had been on strictly salmon based diet for past year, but they recommended changing/rotating protein sources (now beef and venison) changed a few weeks ago and he is eating better.

Coughing?: No
Sneezing?: Yes
Vomiting: No
Polyuria: No
Polydipsia: No
Diarrhea?: No
Diet?: Was on Go Fresh limited ingredient salmon diet for about a year. A few weeks ago switched to Go Fresh venison and Fresh Now beef, with a raw patty at lunchtime (o unsure brand- something with two people's names)

Appetite: Normal
Any collapses or seizures?: Yes

Current Medications

Do you need any refills today?: No
First Cardiac Evaluation?: Yes
Referral Radiographs?: No

Physical Exam

B6

Echocardiogram

Two Dimensional Description: Given B6 history of panicked flailing on the echo table- we gave him B6 prior to echo. This provided ample/heavy sedation (next time could try without or give 1/2 that dose).

The left atrium is severely enlarged. The mitral valve appears normal. The left ventricular chamber is moderately dilated with mildly thin walls and severely globally depressed wall motion. The aortic root appears mildly small (breed variant) with normal aortic valve. The right atrium is moderately dilated. The tricuspid valve appears normal. The right ventricular chamber is mildly dilated. The pulmonary artery and pulmonic valve are normal.

B6

B6

ECHOCARDIOGRAPHIC DIAGNOSIS:

ECHOCARDIOGRAPHIC DIAGNOSIS:
-Dilated cardiomyopathy (severe), r/o idiopathic, secondary to taurine-deficiency, myocarditis, other
-Borderline pulmonary hypertension
-Mildly elevated left ventricular outflow tract velocity (dx 6/2016)

Comparison to previous studies:
There has been significant increase in left atrial size (from 3.86 cm on 2D one year ago), in left ventricular size (from 4.38 cm one year ago) and decrease in %FS (from 30.8% one year ago). MR and TR are new (suspect secondary to annular stretch). The right atrium and ventricle subjectively appear somewhat enlarged as well.

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Other Findings: ECG recording throughout the echo study showed normal sinus arrhythmia at 65-95 bpm (mostly ~70 bpm) with no ventricular ectopy recorded.

ELECTROCARDIOGRAPHIC DIAGNOSIS:
Normal sinus arrhythmia

Blood Pressure

Blood Pressure: 114/71 (84) mmHg (ave of 2 readings- very relaxed, snoozing with sedation on echo table)
Technique: petMAP
Cuff size: 5.5 cm
Site: Right front leg

Final Assessment

Final Diagnosis:
-Dilated cardiomyopathy (severe), r/o idiopathic, secondary to taurine-deficiency, myocarditis, other
-Borderline pulmonary hypertension
-Mildly elevated left ventricular outflow tract velocity (dx 6/2016)
-Normal sinus arrhythmia with no ventricular ectopy

Diagnostic Recommendations:

B6

Therapeutic Recommendations:

B6

Follow-Up:
Recheck 3 months with echocardiogram +/- thoracic radiographs (scheduled for September 11 at 9:30 am)

Consulting Cardiologis B6 DACVIM (cardiology)

06/07/17 01:49:49 888-433-9 -> 0 B6 I Page 001

B6

Owner: B6
Patient:
Species: CANINE
Breed: BOXER
Age: 1Y7M
Gender: MN

Requisition #: 105080834
Accession #: B6
Order recv'd: 06/06/2017
Ordered by: B6
Reported: 06/07/2017

OVA AND PARASITES 3 OR MORE	
OVA & PARASITES	
NO OVA OR PARASITES SEEN CYNICLOMYCES GUTTULATUS ALSO KNOWN AS SACCHAROMYCOPSIS GUTTULATA (NON-PATHOGENIC YEAST) PRESENT	
In cases of acute or chronic diarrhea in addition to a fecal floatation and antigen testing for ova and parasites consider testing for viral, bacterial and protozoal infectious agents using RealPCR (canine diarrhea panel: test code 2625; feline diarrhea panel: test code 2627).	

B6
06/07/2017

FINAL REPORT

14/01/2017 8:27 PM IDEXXSLS → AD80406

D 1

B6

Owner: B6
Patient:
Species: CANINE
Breed: BOXER
Age: B6
Gender: M

Requisition #: 103179571
Accession #: B6
Order recv'd: 01/12/2017
Ordered by: B6
Reported: 01/14/2017

URINE CULT & SUSCEPTIBILITY	
Test	Result
SOURCE:	B6
STATUS:	
COMPLETED CULTURE RESULTS	

URINALYSIS & C+S (MIC)	URINALYSIS			
Test	Result	Reference Range	Flag	Bar Graph

B6
01/14/2017

FINAL REPORT

B6

DISCHARGE SUMMARY
Friday, January 13, 2017

B6
CANINE, BOXER

1. Confinement: _X__ Keep B6 on a leash or in the house for 7 days.
_X__ Do not bring to groomer or allow swimming for 7 days.

2. Food and Water: _X__ For this evening offer half of his usual meal and small amounts of water. Resume his regular diet tomorrow.

3. Sutures/Staples/Drains/Wicks:
_X__ Sutures will dissolve and need not be removed.

4. Special Instructions:
_X__ Monitor incision site daily for any redness, swelling or discharge.
_X__ Discourage from licking or scratching incision site.
_X__ Use E-Collar, especially when unsupervised.
_X__ Give medications as directed. Start pain meds (B6) and restart antibiotics B6 Sat (1/14) a.m.
_X__ Dr. B6 will call you with his final urine culture results.
_X__ If B6 develops any vomiting or diarrhea, please stop giving the B6 and call the office to let us know.

** Your pet had a procedure that may make them groggy for 24-48 hours. If you have any questions or concerns please feel free to call the office.

Anesthesia Monitoring

Date: 1/13/17	Client Name: B6		Pet Name: B6		
Procedure: Neuter	Breed: Boxer	Age: B6	Sex: M	Wt: 66.9#	

Dr: B6 Tech: B6	IV Fluid Type: LRS	Fluid Rate 300 ml hr	Fluid Total 182cc	
Pre op meds:				

B6

Rimadyl 2 ml SQ given @ 9:10 AM
Buprenex 0.8 ml SQ/IV/IM given @ 9:25 AM
Additional Injections: _____

Nail Trim [X] (slight trim) short already

Microchip (Yes) / No / already has [X]

Comments:

rDVM B6 HX 6/16/16-6/24/17 (B6 Echo 6/19/17)

01/12/17 17:01:51 B6 -> 0 I[illegible]x Laboratories I Page 001

B6

B6

Account: 80406

Owner: B6
Patient:
Species: CANINE
Breed: BOXER
Age: B6
Gender: MI

Requisition #:
Accession #: B6
Order recv'd: 01/12/2017
Ordered by: B6
Reported: 01/12/2017

NOTE FROM: B6

NOTE
Your microbiology sample has been received. Results to follow upon completion.

UA COMPLETION

Test	Result
COLLECTION METHOD	
COLOR	
CLARITY	
SPECIFIC GRAVITY	
GLUCOSE	
BILIRUBIN	
KETONES	
BLOOD	
PH	
PROTEIN	
Protein test is performed a test.	
WBC	
RBC	
BACTERIA	
EPI CELL	
MUCUS	
CASTS	
CRYSTALS	
OTHER	
SPERM PRESENT	
UROBILINOGEN	

B6

B6
01/12/2017

FINAL REPORT

PAGE 1 OF 1

01/06/17 07:55:30 B6 -> 0 Idexx Laboratories I Page 001

B6

B6

Account: 80406

Owner: B6
Patient:
Species: CANINE
Breed: BOXER
Age: B6
Gender: MI

Requisition #: B6
Accession #:
Order recv'd: 01/06/2017
Ordered by: B6
Reported: 01/06/2017

YOUNG ADULT PROFILE	CHEM 11 W/ SDMA				
Test	Result				
ALP	B6		(5 - 160) U/L		B6
ALT			(18 - 121) U/L		
ALBUMIN			(2.7 - 3.9) g/dL		
TOTAL PROTEIN			(5.5 - 7.5) g/dL		
GLOBULIN			(2.4 - 4.0) g/dL		
TOTAL BILIRUBIN			(0.0 - 0.3) mg/dL		
BUN			(9 - 31) mg/dL		
CREATININE			(0.5 - 1.5) mg/dL		
GLUCOSE			(63 - 114) mg/dL		
ALB/GLOB RATIO			(0.7 - 1.5)		
BUN/CREATININE RATIO					
HEMOLYSIS INDEX					
Index of N, 1+, 2+ exhibits no significant effect on chemistry values.					
LIPEMIA INDEX	N				
Index of N, 1+, 2+ exhibits no significant effect on chemistry values.					
SDMA	B6		(0 - 14) ug/dL		B6
BOTH SDMA AND CREATININE ARE WITHIN THE REFERENCE INTERVAL which indicates kidney function is likely good. If SDMA and/or creatinine is at the upper end of the reference interval, early kidney disease cannot be ruled out. Evaluate a complete urinalysis to confirm there is no other evidence of kidney disease.					

YOUNG ADULT PROFILE	CBC COMPREHENSIVE				
Test	Result				
WBC	B6		(4.9 - 17.6) K/uL		B6
RBC			(5.39 - 8.70) M/uL		
HGB			(13.4 - 20.7) g/dL		
HCT			(38.3 - 56.5) %		
MCV			(59 - 76) fL		
MCH			(21.9 - 26.1) pg		

B6
01/06/2017

FINAL REPORT - CONTINUED ON NEXT PAGE

PAGE 1

MCHC	B6		(32.6 - 39.2) g/dL		B6
% RETICULOCYTE			%		
RETICULOCYTE			**(10 - 110) K/uL**	H	
RETICULOCYTE COMMENT					

In nonanemic dogs, a reticulocyte count of greater than 110 K/uL of blood may be a transient physiologic response or evidence of bone marrow response to an increased peripheral demand. A persistent reticulocyte count >110 K/uL may indicate occult blood loss, underlying hemolytic disease or disorder that causes an absolute erythrocytosis. Serial monitoring of the erythrogram and reticulocyte count may help determine the significance of this finding.
The following chart can be used as a guideline to determine the degree of regenerative response.
Degree of bone marrow response (K/uL):

Mild	110-150
Moderate	150-300
Marked	>300

% NEUTROPHIL	B6		%		B6
% LYMPHOCYTE			%		
% MONOCYTE			%		
% EOSINOPHIL			%		
% BASOPHIL			%		
PLATELET			(143 - 448) K/uL		
REMARKS					

SLIDE REVIEWED MICROSCOPICALLY.
NO PARASITES SEEN

NEUTROPHIL	B6		(2940 - 12670) /uL		B6
LYMPHOCYTE			(1060 - 4950) /uL		
MONOCYTE			(130 - 1150) /uL		
EOSINOPHIL			(70 - 1490) /uL		
BASOPHIL			(0 - 100) /uL		

HEARTWORM AG ELISA AO	
HEARTWORM ANTIGEN - ELISA	NEGATIVE

The American Heartworm Society recommends that a confirmatory test be run on all positive antigen test results prior to therapy, especially when a positive test result is unexpected. For a positive result on a Heartworm Antigen by ELISA, we recommend submission of a new sample for a second Heartworm Antigen by ELISA (test code 723) as a confirmatory test.

B6

B6

Pet: B6
DOB: B6
Breed: Boxer
Sex: M
Color: brindle

B6

Visit Date: June 30, 2016

Dear Dr. B6

Please see the accompanying cardiology report for our mutual patient B6 n. Thank you for the referral and your continued support of B6. Please contact me if you need any more information regarding B6

Sincerely,

B6, DVM, DACVIM (Cardiology)

B6

SOAP - Cardiology

Jun 30, 2016

B6

Patient: B6
Species: Canine
Breed: Boxer
Color: brindle

DOB: B6
Age: B6 Months B6 Old
Sex: M
Tag:

Acc. No: 223669
Doctor: B6
Weight: 55.2 lbs. (25.038 kgs.)

Phone: B6

Weight: 55.2 lbs.

Prior Medical History

B6

Presenting Complaint

B6

Current Medical History

B6

Echocardiogram

Two Dimensional Description: B6 was very nervous, stiff, intermittently flailing on the echo table. Able to complete study with two holders.

The left atrium appears enlarged, although some of this appearance is related to small aortic root

(leaving final impression of equivocal to mild enlargement). The mitral valve is normal. The left ventricular chamber is normal size with normal wall thicknesses and normal wall motion. The aortic root and proximal aorta appear narrow, with no discrete ridges of narrowing in the subaortic region seen. The aortic valve appears normal. The right atrium and ventricle appear equivocally dilated. The tricuspid valve appears normal. The pulmonary artery and pulmonic valve are normal.

2-D Measurements

B6

M-Mode Measurements

B6

Doppler Findings

B6

ECHOCARDIOGRAPHIC DIAGNOSIS:

ECHOCARDIOGRAPHIC DIAGNOSIS:
-Mildly elevated left and right ventricular outflow tract velocities: suspect normal variant +/- very mild aortic stenosis.
-Impression of mild left atrial enlargement: r/o age-related, other variant of undetermined cause

Final Assessment

Final Diagnosis:
-Mildly elevated left and right ventricular outflow tract velocities: suspect normal variant +/- very mild aortic stenosis.
-Impression of mild left atrial enlargement: r/o age-related, other variant of undetermined cause

Diagnostic Recommendations:
No further cardiac testing currently recommended.

Therapeutic Recommendations:
No cardiac medications currently recommended. B6 appears to be a good anesthetic candidate for future neutering. Out of an abundance of caution (regarding possible mild aortic stenosis), recommend perioperative antibiotics, and avoid agents which would promote tachycardia (ie. use anti-cholinergics only if needed for intraop bradycardia).

Follow-Up:
Recheck echocardiogram 1 year.

Consulting Cardiologist: B6 DVM; DACVIM (cardiology)

rDVM B6 HX 6/16/16-6/24/17 (B6 Echo 6/19/17)

B6

OWNER B6 PATIENT B6 TIME ADMITTED: ADMIT DATE 6/10/16

		Date							Total
1. Office	☒ Office Visit	Vogel							
	☐ After Hours								
	☐ Forms Completion								
2. Intensive Care	☐								
3. Vaccinations	☐ D, DH, DHLP, R, P, Bord								
	☐ FD, FVRC, P, R, FELV								
4. General Procedures	☐ Anal Sacs								
	☐ Nail Trim								
	☒ Injections	Dexamth							
	☐ Sedation								
	☐ Fluid Therapy								
	☐ IV Cath.								
	☐ EKG								
	☐ Transfusion								
	☐ Catheterization (Urinary)								
	☐ Bandaging/Splints								
	☐ Ear Treatment								
	☐ Special Procedure								
5. Pharmacy	☐ Medication								
	☐								
	☐								
	☐								
	☐ Mass. Sales Tax								
6. Anesthesia	☐ Local								
	☐ General								
7. Radiology	☐ Radiograph								
	☐ Procedure, Ultrasound								
8. Dentistry	☐ Hand Scaling								
	☐ Ultrasonic Scaling								
	☐ Extractions								
9. Surgery	☐								
10. Hospitalization	☒ Ward Fee	Yday	15						
	☐ Prof. Daily Care								
	☐ Other								
11. Laboratory	☐ Azostix								
	☐ Fecal Flot./Dig.								
	☐ Blood, HW, FELV test								
	☐ Profile								
	☐ CBC Hematology								
	☐ HT, Wbc, Bun. Glucose, etc.								
	☐ ACTH stim.								
	☐ Urine screen								
	☐ Urinalysis								
	☐ Skin scraping								
	☐ Culture – Sensitivity								
	☐ Biopsy – Cytology								
	☐ Collection Fee								
	☐ Other								
12. Miscellaneous	☐ Euthanasia/cremation								
	☐ Bath								
	☐								
	☐								
								Total	

B6

B6

Pet: B6
DOB: B6
Breed: Boxer
Sex: M
Color: brindle

B6

Visit Date: B6

Dear Colleague,

B6

Sincerely,

B6 DVM
Emergency/Critical Care service

B6

SOAP - Text

Mar 29, 2016

B6

Patient: B6
Species: Canine
Breed: Boxer
Color: brindle
Doctor: B6

DOB: B6
Age: B6 Months B6 Old
Sex: M
Tag:
Weight: 28.881 lbs. (13.1 kgs.)

Panting: No
Is this patient presenting for trauma?: No

Patient Result - Text: History: 5-6 months old; o has had since puppy. UTD on vaccines. On HW preventative, not yet on flea/tick preventative. No travel history, from B6 Here previously for pneumonia; also hx of murmur which appears to have resolved at last vet visit. Diet: Fresh now large breed puppy food.
Current/chronic meds/supplements: none

B6

B6

B6, DVM

Assessment

Problem List

Patient Problem List:

No problems found for period.

Diagnosis

Patient Diagnosis:

No diagnosis found for period.

B6

Client Name: B6
Animal Name:
Client Phone:
MRN: 1373024
Species: Canine
Breed: Boxer
DOB: B6 Sex: M

Doctor:
Clinic: B6
Phone:
Fax:

Accession: B6
Collected: 2/12/2016
Received: 2/16/2016
Approval Date: 2/16/2016 12:27 PM

W Nova Basic Panel

	Ref. Range/Males	2/12/2016 11:09 AM
N NA	142.0-150.0 mmol/L	B6
N K	3.62-4.60 mmol/L	
N CL	112.7-118.3 mmol/L	
N iCA	1.15-1.34 mmol/L	
N GLU	75-116 mg/dl	
N LACT	0.70-2.80 mmol/L	
N BUN	8-30 mg/dl	
N TCO2	mmol/L	
N CREAT	0.6-1.6 mg/dl	
N BUN/CREAT	calc	
N OSMO	mOsm/kg	

Accession number: B6
END OF REPORT (Final)

B6

B6

Pet: B6
DOB: B6
Breed: Boxer
Sex: M
Color: brindle

Admission Date: <CheckedIn

Discharge Date: 2/13/2016

Attending Doctor: B6 DVM

Presenting Problem(s): Cough, difficulty breathing, diarrhea

B6

Thank you for bringing B6 to B6 ! He is a total sweetheart and we are so happy that he is feeling better! Please do not hesitate to contact us with any questions or concerns.

Sincerely,

B6 DVM
DVM

B6

B6

Pet: B6
DOB: B6
Breed: Boxer
Sex: M
Color: brindle

B6

Visit Date: February 12, 2016

B6

Thank you for the referral and your continued support of B6. Please contact me if you need any more information regarding B6

B6

B6

SOAP - Text

Feb 13, 2016

B6

Patient: B6
Species: Canine
Breed: Boxer
Color: brindle
DOB: B6
Age:
Sex: M
Tag:
Acc. No: B6
Doctor: B6
Weight: 28.881 lbs. (13.1 kgs.)
Phone: B6

Weight: 13.1 kgs.
Temperature: 101.6
Pulse: 140
Respiration: 28
Panting: No
Is this patient presenting for trauma?: No

B6

B6

Plan:
1. Discharge today with oral medications

B6 DVM

Assessment

Problem List

Patient Problem List:

Bronchopneumonia - Feb 12, 2016
Diarrhea - Feb 12, 2016

Diagnosis

Patient Diagnosis:

No diagnosis found for period.

B6

B6

Pet: B6
DOB: B6
Breed: Boxer
Sex: M
Color: brindle

B6

Visit Date: February 12, 2016

Dear Colleagues,

B6

Weight: 12.9 lbs.

Presenting Complaint

B6

Physical Exam/Objective

B6

Assessment

B6

B6

B6

improvement by tomorrow. Owner OK with plan.

B6 DVM

B6

B6

Pet: B6
DOB: G B6
Breed: Boxer
Sex: M
Color: brindle

B6

Visit Date: February 12, 2016

B6

Thank you for the referral and your continued support of B6 r. Please contact me if you need any more information regarding B6

B6 DVM

B6

B6

B6

Client Name:
Animal Name: B6
Client Phone:
MRN: 1373024
Species: Canine
Breed: Boxer
DOB: B6 Sex: M

Doctor:
Clinic: B6
Phone
Fax

Accession: B6
Collected: 2/12/2016
Received: 2/12/2016
Approval Date: 2/12/2016 10:49 AM

CBC (Complete Blood Count)

	Ref. Range/Males	2/12/2016 8:16 AM	
WBC	6.0-14.3 K/uL		B6
RBC	5.8-8.9 M/uL	L	
HGB	14.3-21.1 g/dL	L	
HCT	41.7-58.1 %	L	
MCV	63.2-76.8 fL		
MCH	22.9-26.6 pg	L	
MCHC	32.4-38.4 g/dL		
CH	22.2-26.0 pg		
CHCM	31.6-38.9 g/dl		
RDW	10.8-14.9 %		
Platelet Count	161-513 K/uL		

02/12/16 10:48 AM Large platelets seen.

PCT	0.129-0.403 %	B6
MPV	7.5-15.7 FL	
PDW	51.0-73.0 %	
NEU #	3.3-10.1 K/uL	
LYM #	1.0-3.9 K/uL	
MON #	0.1-0.9 K/uL	
EOS #	0.0-1.2 K/uL	
BASO #	0.0-0.1 K/uL	
RBC MORPHOLOGY:		
ANISOCYTOSIS		

Reticulocytes

RETIC Percent	%	B6
RETIC ABSOLUTE Count	x 10^9/L	
RETIC CORRECTED C	%	

02/12/16 9:56 AM Canine Regeneration: Corrected retic >1.0% and Absolute count >80 x 10^9/L

Accession number B6
END OF REPORT (Final)

From:	Rotstein, David </O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0A3B17EBFCF14A6CB8E94F322906BADD-DROTSTEI>
To:	Carey, Lauren; Ceric, Olgica; Glover, Mark; Jones, Jennifer L; Nemser, Sarah; Palmer, Lee Anne; Peloquin, Sarah; Queen, Jackie L; Rotstein, David
Sent:	10/1/2018 8:56:50 PM
Subject:	Decreased contractility with MRx-FW: Honest Kitchen Grain Free beef (love): Lisa Freeman - EON-367344
Attachments:	2055558-report.pdf; 2055558-attachments.zip

David Rotstein, DVM, MPVM, Dipl. ACVP
CVM Vet-LIRN Liaison
CVM OSC/DC/CERT
7519 Standish Place
240-506-6763 (BB)

From: PFR Event <pfreventcreation@fda.hhs.gov>
Sent: Monday, October 01, 2018 4:53 PM
To: Cleary, Michael * <Michael.Cleary@fda.hhs.gov>; HQ Pet Food Report Notification <HQPetFoodReportNotification@fda.hhs.gov>; **B6**
Subject: Honest Kitchen Grain Free beef (love): Lisa Freeman - EON-367344

A PFR Report has been received and PFR Event [EON-367344] has been created in the EON System.

A "PDF" report by name "2055558-report.pdf" is attached to this email notification for your reference. Please note that all documents received in the report are compressed into a zip file by name "2055558-attachments.zip" and is attached to this email notification.

Below is the summary of the report:

EON Key: EON-367344
ICSR #: 2055558
EON Title: PFR Event created for Honest Kitchen Grain Free beef (love) fish (zeal) chicken (force) or turkey (keen). Also Instinct raw beef patties; 2055558

AE Date	09/19/2018	**Number Fed/Exposed**	1
Best By Date		**Number Reacted**	1

Animal Species	Dog	**Outcome to Date**	Stable
Breed	Retriever - Golden		
Age	B6 Years		
District Involved	PFR-New England DO		

Product information
Individual Case Safety Report Number: 2055558
Product Group: Pet Food
Product Name: Honest Kitchen Grain Free beef (love), fish (zeal), chicken (force), or turkey (keen). Also, Instinct raw beef patties
Description: Eating grain-free diet so owner wanted baseline echo. No clinical signs Echo showed no overt DCM but reduced contractility. Taurine low (plasma B6 WB= B6 Recommended diet change and taurine supplementation
Submission Type: Initial
Report Type: Adverse Event (a symptom, reaction or disease associated with the product)
Outcome of reaction/event at the time of last observation: Stable
Number of Animals Treated With Product: 1
Number of Animals Reacted With Product: 1

Product Name	Lot Number or ID	Best By Date
Honest Kitchen Grain Free beef (love), fish (zeal), chicken (force), or turkey (keen). Also, Instinct raw beef patties		

Sender information
Lisa Freeman
200 Westboro Rd
North Grafton, MA 01536
USA

Owner information
B6
USA

To view this PFR Event, please click the link below:
https://eon.fda.gov/eon//browse/EON-367344

To view the PFR Event Report, please click the link below:
https://eon.fda.gov/eon//EventCustomDetailsAction!viewReport.jspa?decorator=none&e=0&issueType=12&issueId=384258

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This email and attached document are being provided to you in your capacity as a Commissioned Official with the U.S. Department of Health and Human Services as authorized by law. You are being provided with this information pursuant to your signed Acceptance of Commission.

This email message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential. Any dissemination, distribution, or copying is strictly prohibited.

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Failure to adhere to the above provisions could result in removal from the approved distribution list. If you think you received this email in error, please send an email to FDAReportableFoods@fda.hhs.gov immediately.

Report Details - EON-367344

ICSR:	2055558		
Type Of Submission:	Initial		
Report Version:	FPSR.FDA.PETF.V.V1		
Type Of Report:	Adverse Event (a symptom, reaction or disease associated with the product)		
Reporting Type:	Voluntary		
Report Submission Date:	2018-10-01 16:39:24 EDT		
Reported Problem:	**Problem Description:**	Eating grain-free diet so owner wanted baseline echo. No clinical signs Echo showed no overt DCM but reduced contractility. Taurine low (plasma B6 WB= B6 Recommended diet change and taurine supplementation	
	Date Problem Started:	09/19/2018	
	Concurrent Medical Problem:	No	
	Outcome to Date:	Stable	
Product Information:	**Product Name:**	Honest Kitchen Grain Free beef (love), fish (zeal), chicken (force), or turkey (keen). Also, Instinct raw beef patties	
	Product Type:	Pet Food	
	Lot Number:		
	Product Use Information:	**Description:**	See diet history
	Manufacturer /Distributor Information:		
	Purchase Location Information:		
Animal Information:	**Name:**	B6	
	Type Of Species:	Dog	
	Type Of Breed:	Retriever - Golden	
	Gender:	Female	
	Reproductive Status:	Neutered	
	Weight:	25.9 Kilogram	
	Age:	B6 Years	
	Assessment of Prior Health:	Excellent	
	Number of Animals Given the Product:	1	
	Number of Animals Reacted:	1	
	Owner Information:	**Owner Information provided:**	Yes
		Contact:	**Name:** B6
			Phone:
			Email:
		Address:	B6 United States
	Healthcare Professional Information:	**Practice Name:**	Tufts Cummings School of Veterinary Medicine
		Contact:	**Name:** Lisa Freeman
			Phone: (508) 887-4523
			Email: lisa.freeman@tufts.edu
		Address:	

			200 Westboro Rd North Grafton Massachusetts 01536 United States
Sender Information:	**Name:**	Lisa Freeman	
	Address:	200 Westboro Rd North Grafton Massachusetts 01536 United States	
	Contact:	**Phone:**	5088874523
		Email:	lisa.freeman@tufts.edu
	Permission To Contact Sender:	Yes	
	Preferred Method Of Contact:	Email	

Additional Documents:

Attachment:	rdvm records.pdf
Description:	RDVM records
Type:	Medical Records
Attachment:	B6 diet history 9-19-18.pdf
Description:	Diet history
Type:	Medical Records
Attachment:	cardio discharge.pdf
Description:	Cardio discharge
Type:	Medical Records
Attachment:	echo 9-19-18.pdf
Description:	Echo
Type:	Echocardiogram
Attachment:	taurine B6 .jpg
Description:	Taurine results
Type:	Laboratory Report

Cummings
Veterinary Medical Center
AT TUFTS UNIVERSITY

Foster Hospital for Small Animals
55 Willard Street
North Grafton, MA 01536
Telephone (508) 839-5395
Fax (508) 839-7951
http://vetmed.tufts.edu/

Discharge Instructions

Patient
Name: B6
Species: Canine
Blonde Female (Spayed) Golden Retriever
Birthdate: B6

Owner
Name: B6
Address: B6

Patient ID: B6

Attending Cardiologist:
☐ John E. Rush DVM, MS, DACVIM (Cardiology), DACVECC
B6

Cardiology Resident:
B6

Cardiology Technician:
B6

Date: 9/19/2018

Diagnoses:
Thank you for bringing B6 to see us for her cardiology evaluation since she has been eating grain free dog food. We did an echocardiogram and found that B6 does not have any major changes to her heart, but she does have mildly reduced contractile function. There is some normal variation in dogs, so it is hard to say if this is clearly something that could be related to diet or if it could just be her normal.

We submitted Taurine levels today, and should have those results within 2 weeks. We will plan to call you with the results, but if you have not heard from us in 2.5 weeks then feel free to give us a call.

Monitoring at Home:
We don't expect any concerns related to B6 heart at this time, but please call if you notice any trouble breathing, coughing, or collapse.

Diet Suggestions:
We recommend feeding a main-stream brand, non-grain-free diet. Dry options that our nutritionist recommends are Royal Canin Early Cardiac, Royal Canin Boxer, or Purina ProPlan Adult Weight Management. B6 heart changes are very mild, so she would not be restricted to one of these diets as long as it is from a large company such as Purina, Royal Canin, or Hills.

If you are struggling to find a diet that B6 does well on then you can schedule a nutrition consult with Dr Lisa Freeman or one of the other Tufts Nutritionists.

Exercise Recommendations:
B6 can continue to have normal exercise and activity.

Recommended Medications:
You could consider supplementing with taurine. B6 dose would be 500mg by mouth twice daily. We recommend Swanson, NOW, or GNC brands, and you can get this over the counter from a vitamin store.

Recheck Visits: A recheck visit is recommened in 6-12 months. At this visit we would recheck the contractile function of B6 heart, and decide if continued cardiology rechecks are necessary.

Thank you for entrusting us with B6 care. She is such a sweet girl! Please contact our Cardiology liaison at (508)-887-4696 or email us at cardiovet@tufts.edu for scheduling and non-emergent questions or concerns.

Please visit our HeartSmart website for more information
http://vet.tufts.edu/heartsmart/

Prescription Refill Disclaimer:
For the safety and well-being of our patients, your pet must have had an examination by one of our veterinarians within the past year in order to obtain prescription medications.

Ordering Food:
Please check with your primary veterinarian to purchase the recommended diet(s). If you wish to purchase your food from us, please call 7-10 days in advance (508-887-4629) to ensure the food is in stock. Alternatively, veterinary diets can be ordered from online retailers with a prescription/veterinary approval.

Clinical Trials:
Clinical trials are studies in which our veterinary doctors work with you and your pet to investigate a specific disease process or a promising new test or treatment. Please see our website: vet.tufts.edu/cvmc/clinical-studies

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Cummings
Veterinary Medical Center
AT TUFTS UNIVERSITY
Cardiology Liaison: 508-887-4696

B6

Patient ID: B6
B6 Canine
B6 Years Old Female (Spayed) Golden Retriever
Blonde

Cardiology Appointment Report

Date: 9/19/2018

Attending Cardiologist:
☐ John E. Rush DVM, MS, DACVIM (Cardiology), DACVECC
B6

Cardiology Resident:
B6

Cardiology Technician:
B6

Student: None

Presenting Complaint: Would like a base-line echo because she has been on a grain free diet. Has been on raw (Instinct) as well. Is on heartworm prev.

Concurrent Diseases: Front legs will shake sometimes when she is standing or lying down. No clear cause or associations. Passes on own.

General Medical History:

Diet and Supplements: Honest Kitchen - fish, beef, turkey, chicken gives her itchy feet. Previously Instinct Raw. When puppy Taste of the Wild.

Cardiovascular History:
Prior CHF diagnosis? no
Prior heart murmur? no
Prior ATE? no
Prior arrhythmia? no
Monitoring respiratory rate and effort at home? no
Cough? no
Shortness of breath or difficulty breathing? no
Syncope or collapse? no
Sudden onset lameness? no
Exercise intolerance? no

Current Medications Pertinent to CV System:
None

Cardiac Physical Examination:

B6

Muscle condition:
- [x] Normal
- [ ] Mild muscle loss
- [ ] Moderate cachexia
- [ ] Marked cachexia

Cardiovascular Physical Exam:

Murmur Grade:
- [x] None
- [ ] I/VI
- [ ] II/VI
- [ ] III/VI
- [ ] IV/VI
- [ ] V/VI
- [ ] VI/VI

Jugular vein:
- [x] Bottom 1/3 of the neck
- [ ] Middle 1/3 of the neck
- [ ] 1/2 way up the neck
- [ ] Top 2/3 of the neck

Arterial pulses:
- [ ] Weak
- [ ] Fair
- [x] Good
- [ ] Strong
- [ ] Bounding
- [ ] Pulse deficits
- [ ] Pulsus paradoxus
- [ ] Other:

Arrhythmia:
- [x] None
- [ ] Sinus arrhythmia
- [ ] Premature beats
- [ ] Bradycardia
- [ ] Tachycardia

Gallop:
- [ ] Yes
- [x] No
- [ ] Intermittent
- [ ] Pronounced
- [ ] Other:

Pulmonary assessments:
- [x] Eupneic
- [ ] Mild dyspnea
- [ ] Marked dyspnea
- [x] Normal BV sounds
- [ ] Pulmonary crackles
- [ ] Wheezes
- [ ] Upper airway stridor

Abdominal exam:
- [x] Normal
- [ ] Hepatomegaly
- [ ] Abdominal distension
- [ ] Mild ascites
- [ ] Marked ascites

Problems:
Grain free diet

Diagnostic plan:

- [x] Echocardiogram
- [ ] Chemistry profile
- [ ] ECG
- [ ] Renal profile
- [ ] Blood pressure
- [ ] Dialysis profile
- [ ] Thoracic radiographs
- [ ] NT-proBNP
- [ ] Troponin I
- [ ] Other tests:

Echocardiogram Findings:

B6

Mitral inflow:

- [ ] Summated
- [ ] Normal
- [x] Delayed relaxation
- [ ] Pseudonormal
- [ ] Restrictive

ECG findings:

B6

Assessment and recommendations:

Echocardiogram reveals mildly reduced contractile function, but no overt evidence of DCM such as wall thinning or LV or LA dilation. Taurine whole blood and plasma submitted today.

B6

B6

Final Diagnosis:

Grain free diet

Mildly reduced contractile function (r/o nutritional induced early cardiomyopathy v variation of normal)

M-Mode		
IVSd	B6	cm
LVIDd		cm
LVPWd		cm
IVSs		cm
LVIDs		cm
LVPWs		cm
%FS		%
Max LA		cm
TAPSE		cm
EPSS		cm

M-Mode Normalized		
IVSdN	B6	(0.29 - 0.52)
LVIDdN		(1.35 - 1.73)
LVPWdN		(0.33 - 0.53)
IVSsN		(0.43 - 0.71) !
LVIDsN		(0.79 - 1.14)
LVPWsN		(0.53 - 0.78)

2D		
SA LA	B6	cm
Ao Diam		cm
SA LA / Ao Diam		
IVSd		cm
LVIDd		cm
LVPWd		cm
EDV(Teich)		ml
IVSs		cm
LVIDs		cm
LVPWs		cm
ESV(Teich)		ml
EF(Teich)		%
%FS		%
SV(Teich)		ml
LVId LAX		cm
LVAd LAX		cm
LVEDV A-L LAX		ml
LVEDV MOD LAX		ml
LVLs LAX		cm
LVAs LAX		cm
LVESV A-L LAX		ml
LVESV MOD LAX		ml
HR		BPM
EF A-L LAX		%
LVEF MOD LAX		%
SV A-L LAX		ml
SV MOD LAX		ml
CO A-L LAX		l/min
CO MOD LAX		l/min

Doppler		
MV E Vel	B6	m/s
MV DecT		ms
MV A Vel		m/s
MV E/A Ratio		
E'		m/s
A'		m/s
E/E'		
PV Vmax		m/s

PV maxPG	B6	mmHg
AV Vmax		m/s
AV maxPG		mmHg

CARDIOLOGY DIET HISTORY FORM

Please answer the following questions about your pet

Pet's name: **B6** Owner's name: **B6** Today's date: 9/19/18

1. How would you assess your pet's appetite? (mark the point on the line below that best represents your pet's appetite)

Example: Poor _____ | _____ Excellent

Poor _____ Excellent

2. Have you noticed a change in your pet's appetite over the last 1-2 weeks? (check all that apply)

☒ Eats about the same amount as usual ☐ Eats less than usual ☐ Eats more than usual
☐ Seems to prefer different foods than usual ☐ Other _____

3. Over the last few weeks, has your pet (check one)

☐ Lost weight ☐ Gained weight ☒ Stayed about the same weight ☐ Don't know

4. Please list below ALL pet foods, people food, treats, snack, dental chews, rawhides, and any other food item that your pet currently eats. Please include the brand, specific product, and flavor so we know exactly what you pet is eating.

Food (include specific product and flavor) **Form** **Amount** **How often?** **Fed since**

Examples are shown in the table – please provide enough detail that we could go do the store and buy the exact same food.

Food (include specific product and flavor)	Form	Amount	How often?	Fed since
Nutro Grain Free Chicken, Lentil, & Sweet Potato Adult	*dry*	*1 ½ cup*	*2x/day*	*Jan 2018*
85% lean hamburger	*microwaved*	*3 oz*	*1x/week*	*Jan 2015*
Pupperoni original beef flavor	*treat*	*½*	*1x/day*	*Aug 2015*
Rawhide	*treat*	*6 inch twist*	*1x/week*	*Dec 2015*
INSTINCT RAW BEEF PATTIES	FROZEN PATTY MICROWAVED	1 PATTY	2 X DAY	1 YEAR - 2014
HONEST KITCHEN GRAIN FREE BEEF - "LOVE" GRAIN FREE FISH - "ZEAL" GRAIN FREE CHICKEN - "FORCE" WHOLE GRAIN TURKEY - "KEEN"	DEHYDRATED	1 CUP	2 X DAY	2015 - PRESENT
ZUKES MINI SALMON TREATS	MINI BITES		EVERY DAY	1 YEAR
NATURALLY HEALTHY PETS NEW ZEALAND DEER VELVET ORAL DROPS	2 DROPS		1 X / DAY	1 YEAR

*Any additional diet information can be listed on the back of this sheet

ANTLER BONE

5. Do you give any dietary supplements to your pet (for example: vitamins, glucosamine, fatty acids, or any other supplements)? ☐ Yes ☒ No If yes, please list which ones and give brands and amounts:

			Brand/Concentration	Amount per day
Taurine	☐ Yes	☐ No		
Carnitine	☐ Yes	☐ No		
Antioxidants	☐ Yes	☐ No		
Multivitamin	☐ Yes	☐ No		
Fish oil	☐ Yes	☐ No		
Coenzyme Q10	☐ Yes	☐ No		
Other (please list):				
Example: Vitamin C			*Nature's Bounty*	*500 mg tablets – 1 per day*

6. How do you administer pills to your pet?

☒ I do not give any medications
☐ I put them directly in my pet's mouth without food
☐ I put them in my pet's dog/cat food
☐ I put them in a Pill Pocket or similar product
☐ I put them in foods (list foods): _____

ALSO TASTE OF THE WILD DRY AS A PUPPY (CAME FROM BREEDER ON THIS DIET)

From: Related PFR Event <pfrsignificantactivitycreation@fda.hhs.gov>

To: Rotstein, David; Cleary, Michael *; HQ Pet Food Report Notification; B6

Sent: 6/10/2019 8:20:57 PM

Subject: Fromm Game Bird Recipe Dog - Four-Star - Dry -Grain-Free formula: B6 B6 EON-390092

Attachments: 2068038-report.pdf; 2068038-attachments.zip

A PFR Report has been received and Related PFR Event [EON-390092] has been created in the EON System.

A "PDF" report by name "2068038-report.pdf" is attached to this email notification for your reference. Please note that all documents received in the report are compressed into a zip file by name "2068038-attachments.zip" and is attached to this email notification.

Below is the summary of the report:

EON Key: EON-390092
ICSR #: 2068038
EON Title: Related PFR Event created for Fromm Game Bird Recipe Dog · Four-Star · Dry Grain-Free formula; 2068038

AE Date	04/16/2019	**Number Fed/Exposed**	1
Best By Date		**Number Reacted**	1
Animal Species	Dog	**Outcome to Date**	Better/Improved/Recovering
Breed	Hound (unspecified)		
Age	B6 ears		
District Involved	PFR-New England DO		

Product information
Individual Case Safety Report Number: 2068038
Product Group: Pet Food
Product Name: Fromm Game Bird Recipe Dog · Four-Star · Dry Grain-Free formula
Description: Patient presented to rDVM for evaluation of abdominal distension x 5 weeks and increase in respiratory rate and effort. FAST scan revealed moderate ascites. Patient was referred to Tufts for further evaluation. Findings consistent with advanced DMVD with suspect L-CHF and poor contractile function.

Considering LA enlargement and severity of MR and AI, we would expect a better systolic function. B6 is recommended. Mild respiratory effort and occasional b-lines vote in favor to L-CHF. There is enough cardiac changes to justify L and R CHF. Since patient is on a BEG diet, it is unclear whether diet is playing a role on decreased contractile function. Recommend transition to a grain-based, low sodium diet and consider Taurine supplementation. Abdominocentesis was performed (5 liters of serous sanguineous fluid) and analysis is recommended. Recommend hospitalization, patient on telemetry monitoring and respiratory watch. Fluid check in the morning and kidney values daily while in the hospital. Since patient is on a BEG diet, recommend transition to a grain-based, low sodium diet.

Submission Type: Followup
Report Type: Adverse Event (a symptom, reaction or disease associated with the product)
Outcome of reaction/event at the time of last observation: Better/Improved/Recovering
Number of Animals Treated With Product: 1
Number of Animals Reacted With Product: 1

Product Name	Lot Number or ID	Best By Date
Fromm Game Bird Recipe Dog · Four-Star · Dry Grain-Free formula		

This report is linked to:
Initial EON Event Key: EON-388971
Initial ICSR: 2067510

Sender information

B6

Owner information

B6 USA

To view this Related PFR Event, please click the link below:
https://eon.fda.gov/eon//browse/EON-390092

To view the Related PFR Event Report, please click the link below:
https://eon.fda.gov/eon//EventCustomDetailsAction!viewReport.jspa?decorator=none&e=0&issueType=10100&issueId=407364&parentIssueTypeId=12

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Report Details - EON-390092

ICSR:	2068038
Type Of Submission:	Followup
Report Version:	FPSR.FDA.PETF.V.V1
Type Of Report:	Adverse Event (a symptom, reaction or disease associated with the product)
Reporting Type:	Voluntary
Report Submission Date:	2019-06-10 16:15:32 EDT
Initial Report Date:	05/28/2019
Parent ICSR:	2067510
Follow-up Report to FDA Request:	Yes

Reported Problem:

Problem Description:	Patient presented to rDVM for evaluation of abdominal distension x 5 weeks and increase in respiratory rate and effort. FAST scan revealed moderate ascites. Patient was referred to Tufts for further evaluation. Findings consistent with advanced DMVD with suspect L-CHF and poor contractile function. Considering LA enlargement and severity of MR and AI, we would expect a better systolic function B6 is recommended. Mild respiratory effort and occasional b-lines vote in favor to L-CHF. There is enough cardiac changes to justify L and R CHF. Since patient is on a BEG diet, it is unclear whether diet is playing a role on decreased contractile function. Recommend transition to a grain-based, low sodium diet and consider Taurine supplementation. Abdominocentesis was performed (5 liters of serous sanguineous fluid) and analysis is recommended. Recommend hospitalization, patient on telemetry monitoring and respiratory watch. Fluid check in the morning and kidney values daily while in the hospital. Since patient is on a BEG diet, recommend transition to a grain-based, low sodium diet.
Date Problem Started:	04/16/2019
Concurrent Medical Problem:	Yes
Pre Existing Conditions:	B6
Outcome to Date:	Better/Improved/Recovering

Product Information:

Product Name:	Fromm Game Bird Recipe Dog · Four-Star · Dry Grain-Free formula
Product Type:	Pet Food
Lot Number:	
Package Type:	BAG
Product Use Information:	
Manufacturer /Distributor Information:	
Purchase Location Information:	

Animal Information:

Name:	
Type Of Species:	Dog
Type Of Breed:	Hound (unspecified)
Gender:	Male
Reproductive Status:	Neutered
Weight:	38.9 Kilogram
Age:	B6 Years
Assessment of Prior Health:	Good
Number of Animals	1

	Given the Product:		
	Number of Animals Reacted:	1	
	Owner Information:	**Owner Information provided:**	Yes
		Contact:	**Name:** B6 **Phone:**
		Address:	B6 United States
	Healthcare Professional Information:	**Practice Name:**	Tufts Cummings School of Veterinary Medicine
		Contact:	**Name:** **Phone:** B6 **Email:**
		Address:	200 Westboro Road North Grafton Massachusetts 01536 United States
		Practice Name:	Tufts University Cummings School of Veterinary Medicine
		Contact:	**Name:** Lisa Freeman **Phone:** (508) 887-4696
		Address:	200 Westboro Road North Grafton Massachusetts 01536 United States
		Permission to Release Records to FDA:	Yes
Sender Information:	**Name:**	B6	
	Address:	200 Westboro Road North Grafton Massachusetts 01536 United States	
	Contact:	**Phone:** **Email:** B6	
	Permission To Contact Sender:	Yes	
	Preferred Method Of Contact:	Email	
	Reported to Other Parties:	None	
Additional Documents:			
	Attachment:	Complete amino acid analysis 5-29-2019.pdf	
	Description:	Lab work	
	Type:	Laboratory Report	
	Attachment:	troponin 5-30-2019.pdf	
	Description:	Lab work	
	Type:	Laboratory Report	

Attachment:	Follow-up medical records.pdf
Description:	Medical Records
Type:	Medical Records

Report of Complete amino acid analysis

Amino Acid Lab, UC Davis, Rm 1020 VM 3B
1089 Veterinary Medicine Drive, Davis, CA 95616
Tel.: 530-752-5058, Email: ucd.aminoacid.lab@ucdavis.edu
www.vetmed.ucdavis.edu/labs/amino-acid-laboratory

Plasma sample from: Tufts Cummings School of Vet Med

Contact: B6

Patient: B6 **Owner:** B6

Date of arrival: 05/23/19; Date of Report: 05/29/19

	Reference data (Mean ± SEM) (nmol/ml)	Measured (nmol/ml) Plasma
L-Alanine	389 ± 9	B6
L-Arginine	102 ± 3	
L-a- Amino - n Butyric Acid	6 ± 2	
L-Asparagine	41 ± 1	
L-Aspartic Acid	7 ± 0.2	
L-Citrulline	41 ± 2	
Cystathionine	3 ± 1	
L-Cystine	46 ± 1	
L-Glutamic Acid	24 ± 1	
L-Glutamine	495 ± 9	
Glycine	266 ± 8	
L-Histidine	71 ± 2	
1 - Methyl-L-histidine		
3 - Methyl-L-histidine	6 ± 1	
L-Isoleucine	51 ± 1	
L-Leucine	120 ± 3	
L-Lysine	131 ± 5	
L-Methionine	57 ± 2	
L-Ornithine	35 ± 2	
L-Phenylalanine	45 ± 1	
L-Proline	249 ± 8	
Hydroxy-L-proline	67 ± 4	
L-Serine	107 ± 3	
Taurine	77 ± 2	
L-Threonine	178 ± 5	
Tryptophan	60 ± 2	
L-Tyrosine	39 ± 1	
L-Valine	158 ± 4	

Reference data were collected from 131 healthy adult dogs of varying body size fed commercially prepared food

Cummings Veterinary Medical Center
AT TUFTS UNIVERSITY

Foster Hospital for Small Animals
55 Willard Street
North Grafton, MA 01536
(508) 839-5395

Client:	B6
Veterinarian:	
Patient ID:	B6
Visit ID:	

Patient:	B6
Species:	Canine
Breed:	Treeing Walker Coonhound
Sex:	Male (Neutered)
Age:	B6 Years Old

Lab Results Report

Chemistry 21 (Cobas) 6/7/2019 2:48:19 PM **Accession ID:** B6

Test	Results	Reference Range	Units
PHOSPHORUS		2.6 - 7.2	mg/dL
GLUCOSE		67 - 135	mg/dL
A/G RATIO		0.7 - 1.6	
OSMOLALITY (CALCULATED)		291 - 315	mmol/L
SODIUM		140 - 150	mEq/L
CHLORIDE		106 - 116	mEq/L
CALCIUM2		9.4 - 11.3	mg/dL
ALBUMIN		2.8 - 4	g/dL
AST	B6	9 - 54	U/L
POTASSIUM		3.7 - 5.4	mEq/L
ALK PHOS		12 - 127	U/L
CHOLESTEROL		82 - 355	mg/dL
UREA		8 - 30	mg/dL
T. PROTEIN		5.5 - 7.8	g/dL
NA/K		29 - 40	
COMMENTS (CHEMISTRY)		0 - 0	
CREATININE		0.6 - 2	mg/dL
ALT		14 - 86	U/L
T BILIRUBIN		0.1 - 0.3	mg/dL

Client:
Patient: B6

GLOBULINS	B6	2.3 - 4.2	g/dL

stringsoft

Printed Monday, June 10, 2019

Vitals Results

6/7/2019 2:04:56 PM	Weight (kg)	37.3000

Patient History

06/07/2019 01:55 PM	UserForm
06/07/2019 01:57 PM	Purchase
06/07/2019 02:04 PM	Vitals
06/07/2019 02:04 PM	Vitals
06/07/2019 02:08 PM	Treatment
06/07/2019 02:35 PM	UserForm
06/07/2019 02:36 PM	Purchase
06/07/2019 02:47 PM	Purchase
06/07/2019 03:33 PM	Prescription

B6

Cummings
Veterinary Medical Center
AT TUFTS UNIVERSITY

Foster Hospital for Small Animals
55 Willard Street
North Grafton, MA 01536
Telephone (508) 839-5395
Fax (508) 839-7951
http://vetmed.tufts.edu/

Discharge Instructions

Patient
Name: B6
Species: Canine
Tricolor Male (Neutered) Treeing Walker Coonhound
Birthdate: B6

Owner
Name: B6
Address: B6

Patient ID: B6

Attending Cardiologist:
☑ John E. Rush DVM, MS, DACVIM (Cardiology), DACVECC
B6

Cardiology Resident:
B6

Cardiology Technician:
B6

Student: B6 V20

Admit Date: 6/7/2019 1:52:55 PM
Discharge Date: 6/7/2019

Diagnoses: Chronic valvular disease with mitral regurgitation, history of congestive heart failure with pulmonary edema and ascites.

Clinical Findings: Thank you for bringing B6 to Tufts for a one week recheck. B6 had a recent episode of heart failure and still had residual fluid in his abdomen during his last visit. You report he has been tolerating his medications very well and has been eating wonderful since last visit! You also noticed his belly has gotten smaller since last visit.

On physical exam today, B6 was bright and alert. He lost about 2kg (4.4lb). As expected, his murmur is unchanged since his last visit. His pulses were good today. We took a quick look at B6 belly with the ultrasound to check for fluid in his abdomen (ascites). B6 ascited has almost completely resolved, indicating that the medications are working great for him!

We have submitted a chemistry panel to recheck B6 kidney values to make sure he is tolerating the B6 well. You should hear back with these results in the next 1-2 business days. Depending on the values, we may consider increase the frequency of the B6 to twice a day.

Monitoring at Home:

***You can evaluate the fluid in his belly by using a malleable measuring tape around the same part of his abdomen every other day. If you notice significant increases in size, this may also mean that you should give an extra dose of** B6 *** Please let us know if additional doses are given.**

We would like you to monitor B6 breathing rate and effort at home, ideally during sleep or at a time of rest. The doses of drugs will be adjusted based on the breathing rate and effort. In general, most dogs with heart failure that is well controlled have a breathing rate at rest of less than 35 breaths per minute. In addition, the breathing effort, noted by the amount of belly wall motion used for each breath, is fairly minimal if heart failure is controlled. An increase in breathing rate or effort will usually mean that you should give an extra dose o B6 If difficulty breathing is not improved within 30-60 minutes after giving extra B6 then we recommend that a recheck exam be scheduled and/or that B6 be evaluated by an emergency clinic. There are instructions for monitoring breathing, and a form to help keep track of breathing rate and drug doses, on the Tufts HeartSmart web site (http://vet.tufts.edu/heartsmart/at-home-monitoring/).

We also want you to watch for weakness or collapse, a reduction in appetite, worsening cough, or distention of the belly as these findings indicate that we should do a recheck examination.

Diet Suggestions: Continue B6 on his early cardiac diet. He is on the thinner side right now so we recommend increasing his food from 4 cups a day to 5 cups a day.

Recommended Medications:

B6

Recheck Visits: B6 as an appointment recheck scheduled for the study he is participating in at 2pm on August 23rd with B6

Thank you for entrusting us with B6 care. Please contact our Cardiology liaison at (508)-887-4696 or email us at cardionet@tufts.edu for scheduling and non-emergent questions or concerns.

Please visit our HeartSmart website for more information
http://vet.tufts.edu/heartsmart/

Prescription Refill Disclaimer:
For the safety and well-being of our patients, your pet must have had an examination by one of our veterinarians within the past year in order to obtain prescription medications.

Ordering Food:
Please check with your primary veterinarian to purchase the recommended diet(s). If you wish to purchase your food from us, please call 7-10 days in advance (508-887-4629) to ensure the food is in stock. Alternatively, veterinary diets can be ordered from online retailers with a prescription/veterinary approval.

Clinical Trials:
Clinical trials are studies in which our veterinary doctors work with you and your pet to investigate a specific disease process or a promising new test or treatment. Please see our website: vet.tufts.edu/cvmc/clinical-studies

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Nutritional Tips for Pets with Heart Disease

Low sodium, high quality pet treats

Notes:

1. Most other dog treats are high in sodium.
2. If your pet has other medical conditions, these treats may not be appropriate. Talk to your veterinarian if you have questions or make an appointment with the Nutrition Service.

Product	Calories per treat
Dogs	
Hill's Science Diet Baked Light Biscuits with Real Chicken Small Dog Treat	8
Hill's Science Diet Baked Light Biscuits with Real Chicken Medium Dog Treat	34
Hill's Science Diet Soft Savories Peanut Butter & Banana, Beef & Cheddar, or Chicken & Yogurt Dog Treat	25-27, depending on flavor
Hill's Ideal Balance Soft-Baked Naturals with Chicken & Carrots, Duck & Pumpkin, or Beef & Sweet Potato Dog Treat	12-13, depending on flavor
Purina Beyond Natural Salmon Dog Biscuit Treat with Oats or Chicken & Barley	27-29, depending on flavor
Purina Alpo Variety Snaps Little Bites (beef, chicken, liver, lamb or beef, bacon, cheese, peanut butter)	16
Purina Alpo Variety Snaps Big Bites (beef, chicken, liver, lamb)	58
Royal Canin Original Canine treat	5
Cats	
Royal Canin Original Feline treat	2
Fancy Feast Duos Natural Rotisserie Chicken Cat treat	2
Fancy Feast Duos Tuna with Accents of Parsley Cat treat	2

Taste enhancers to can make your pet's food tastier to increase food intake

Safe and effective appetite stimulants are now available for dogs and cats. Please talk to your veterinarian if your pet is not eating well, not eating ideal foods, or is losing weight.

Notes:

1. All foods in this list should be prepared without salt
2. These taste enhancers should be added in small amounts. If your pet eats too much of them, they will unbalance the diet and increase your pet's risk for nutritional deficiencies

Dogs

- Honey or maple syrup
- Homemade chicken, beef, or fish broth (made without salt; avoid all deli meats and rotisserie chicken). Avoid store bought broths because even the low sodium brands are too high in sodium.
- Sugar (brown or white) – Domino pourable light brown sugar is a good option
- Vanilla or fruit yogurt – One option that dogs seem to like is Yoplait Custard Yogurt (caramel or vanilla flavors). If you try other brands, just be sure the sodium is less than 100 mg per 100 calories (the Yoplait is 95 mg per 170 calories which comes out to 56 mg sodium per 100 calories). Also avoid yogurts with artificial sweeteners.
- Maple syrup. Low salt brands include Log Cabin All Natural, Maple Grove Farm 100% pure maple syrup, or Stop and Shop Original Syrup
- Applesauce (be sure they have less than 50 mg sodium per serving)
- Ketchup (no salt added). Examples include Hunts or Heinz no salt added
- Pasta sauce (no salt added). Examples: Francesco Rinaldi no salt added or Enrico's no salt added)
- Frosted Mini Wheats Original – these can be crumbled on his food
- Lean meats, cooked (chicken, turkey, beef, or fish) – not deli/sandwich meats/cold cuts, rotisserie chicken, and any canned fish or meat
- Eggs, cooked

Dogs (continued)

- Homemade chicken, beef, or fish broth (even low sodium store-bought broths are too high in sodium). Avoid all canned soups unless labeled as no salt added
- Low-salt breakfast cereal - the label should read, "very low sodium food" or contain less than 20 mg sodium per serving. A good option is Frosted Mini Wheats Original or Little Bites Original
- Fresh vegetables/fruit. Examples include carrots, green beans, apple, orange, banana (avoid grapes, raisins, onions, garlic)
- Low sodium canned dog foods

Cats

- Lean meats, cooked (chicken, turkey, beef, or fish) – not sandwich meats/cold cuts, canned tuna, or rotisserie chicken
- Eggs, cooked
- Homemade chicken, beef, or fish broth (even low sodium store-bought broths are too high in sodium)
- Low sodium canned cat foods

Foods to avoid

- Fatty foods (meat trimmings, cream, ice cream)
- Baby food
- Pickled foods
- Bread
- Pizza
- Condiments (ketchup, soy sauce, barbecue sauce, etc – unless they are unsalted or no salt added)
- Sandwich meats/cold cuts (ham, corned beef, salami, sausages, bacon, hot dogs)
- Rotisserie chicken
- Most cheeses, including "squirtable" cheeses
- Processed foods (such as, potato mixes, rice mixes, macaroni and cheese)
- Canned vegetables (unless "no salt added")
- Potato chips, packaged popcorn, crackers, and other snack foods
- Soups (unless homemade without salt)
- Most commercial pet treats

Tips for administering medications

Foods commonly used to administer your pet's pills can provide a large amount of additional salt to your pet's diet. Preferable ways to give medications include:

- Have one of our staff show you how to give medications without using food
- Insert medications into one of the following foods:

Dogs or cats

- Low-sodium canned pet food
- Home-cooked meat such as chicken or hamburger (made without salt); not lunch meats
- Whipped cream (Reddi Wip)
- Marshmallows
- Greenies Pill Pockets
  - Dog chicken, hickory smoke, or peanut butter flavors; cat chicken or salmon flavor
  - Avoid grain-free duck and pea which is high in sodium
  - Try to use the smallest size possible (ideally, the cat sized Pill Pockets, even for dogs) and as few as possible to avoid excessive salt.
    - Caution: Not all similar products from other companies are low in sodium .

Dogs

- Soft fruit, such as banana, orange, melon, or strawberries (avoid grapes)
- Peanut butter (only if labeled as "no salt added") – examples include Smucker's Natural Creamy Peanut Butter with No Salt Added or Teddie All Natural Smooth Unsalted Butter
- Frosting (should be less than 75 mg/serving and contain no artificial sweeteners or xylitol). Examples include Duncan Hines whipped vanilla frosting, Betty Crocker whipped vanilla frosting)

You may find our Petfoodology post called, "Pill-popping pets" helpful for additional ideas:
http://vetnutrition.tufts.edu/2018/09/foods_for_giving_pills/

Cummings
Veterinary Medical Center
AT TUFTS UNIVERSITY
Cardiology Liaison: 508-887-4696

B6

Patient ID: B6
B6 Canine
Years Old Male (Neutered) Treeing Walker Coonhound
Tricolor

Cardiology Appointment Report

Date: B6

Attending Cardiologist:
☐ John E. Rush DVM, MS, DACVIM (Cardiology), DACVECC

B6

Cardiology Resident:
B6

Cardiology Technician:
B6

Student: B6

Presenting Complaint: Recheck. DMVD with decreased contractile function and recent history of CHF (5/22/19). Persistent mild to moderate ascites during last visit 5/29/19.

Concurrent Diseases:
B6 unknown etiology (saw optho but declined further diagnostics)

General Medical History:
Appetite back to normal, taking medications no problem, less restless, belly seems less distended than last visit. Looks thinner than he was prior to CHF

History of B6
Had loose bowel movements recently but also had change in diet.
Flaky skin
B6

Diet and Supplements:
Royal canin early cardiac- 4 cups a day

Cardiovascular History:
Prior CHF diagnosis? Y
Prior heart murmur? Y- III
Prior ATE? N

Prior arrhythmia? N
Monitoring respiratory rate and effort at home? Y averaging 33
Cough? N
Shortness of breath or difficulty breathing? N
Syncope or collapse? N
Sudden onset lameness? N
Exercise intolerance? N

Current Mediations Pertinent to CV System:

B6

Cardiac Physical Examination:

B6

Muscle condition:

- ☐ Normal
- ☑ Mild muscle loss
- ☐ Moderate cachexia
- ☐ Marked cachexia

Cardiovascular Physical Exam:

Murmur Grade:

- ☐ None
- ☐ I/VI
- ☑ II/VI
- ☑ III/VI
- ☐ IV/VI
- ☐ V/VI
- ☐ VI/VI

Murmur location/description: left apical systolic

Jugular vein:

- ☑ Bottom 1/3 of the neck
- ☐ 1/2 way up the neck

- [ ] Middle 1/3 of the neck
- [ ] Top 2/3 of the neck

Arterial pulses:
- [ ] Weak
- [ ] Fair
- [x] Good
- [ ] Strong
- [ ] Bounding
- [ ] Pulse deficits
- [ ] Pulsus paradoxus
- [ ] Other:

Arrhythmia:
- [x] None
- [ ] Sinus arrhythmia
- [ ] Premature beats
- [ ] Bradycardia
- [ ] Tachycardia

Gallop:
- [ ] Yes
- [x] No
- [ ] Intermittent
- [ ] Pronounced
- [ ] Other:

Pulmonary assessments:
- [x] Eupneic
- [ ] Mild dyspnea
- [ ] Marked dyspnea
- [x] Normal BV sounds
- [ ] Pulmonary crackles
- [ ] Wheezes
- [ ] Upper airway stridor

Abdominal exam:
- [x] Normal
- [ ] Hepatomegaly
- [ ] Abdominal distension
- [ ] Mild ascites
- [ ] Marked ascites

Problems:

CMVD;

Hx of CHF;

Hx of B6

Diagnostic plan:
- [ ] Echocardiogram
- [x] Chemistry profile
- [ ] ECG
- [ ] Renal profile
- [ ] Blood pressure
- [ ] Dialysis profile
- [ ] Thoracic radiographs
- [ ] NT-proBNP
- [ ] Troponin I
- [x] Other tests: fluid check

Echocardiogram Findings:

General/2-D findings: *fluid check*

There is very mild ascites visualized. No pericardial effusion or b-lines seen.

Assessment and recommendations:

Findings consistent with marked improvement on abdominal fluid and, since patient is clinically better with good appetite and energy level, recommend maintain current medications doses and frequency. Since blood work revealed increase in kidney values, B6 instead of increasing to BID. Clients oriented to measure belly twice a week and keep counting respiratory rate. Recommend start fish oil since patient has moderate cachexia. Recheck kidney values and echocardiogram in 2 months, sooner if clinical signs occur such as decreased appetite, lethargy, abdominal distension, or dyspnea.

Final Diagnosis:
DMVD with PHTN;
Reduced contractile function.

Heart Failure Classification Score:
ISACHC Classification:

- ☐ Ia
- ☐ Ib
- ☐ II
- ☑ IIIa
- ☐ IIIb

ACVIM Classification:

- ☐ A
- ☐ B1
- ☐ B2
- ☑ C
- ☐ D

Gastrointestinal Laboratory
Dr. J.M. Steiner
Department of Small Animal Clinical Sciences
Texas A&M University
4474 TAMU
College Station, TX 77843-4474

Website User ID: lisa.freeman@tufts.edu OR B6

GI Lab Assigned Clinic ID: 23523

Dr. Freeman
Tufts Cummings School of Vet Med - Cardiology/Nutrition
200 Westboro Road
North Grafton, MA 01536
USA

Phone: 508 887 4696
Fax:
Animal Name: **B6**
Owner Name:
Species: Canine
Date Received: May 30, 2019

Tufts Cummings School of Vet Med - Cardiology/Nutrition Tracking Number: 309861

GI Lab Accession: B6

Test	Result	Reference Interval	Assay Date
Ultra-Sensitive Troponin I Fasting	**B6** ng/mL	≤0.06	05/31/19

B6

Comments:

GI Lab Contact Information

Phone: (979) 862-2861
Fax: (979) 862-2864
Email: gilab@cvm.tamu.edu
vetmed.tamu.edu/gilab

From:	Reimschuessel, Renate </O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4C00C47AE2794134B2906D6B9252FCF6-RREIMSCH>
To:	lisa.freeman@tufts.edu
Sent:	7/17/2018 3:48:03 PM
Subject:	800.267-FDA Case Investigation for B6 (EON-358523)
Attachments:	02-Vet-LIRN-NetworkProceduresVets-12.22.2015.pdf; 03-Vet-LIRN-Network ProceduresOwners-12.22.2015.pdf

Dear Dr. Freeman,
Thank you for submitting your consumer complaint to FDA. I'm sorry to hear about B6 illness.
As part of our investigation, we'd like to request:

- **Full Medical Records**
  - Please email (preferred) or fax (301-210-4685) a copy of B6 **entire** medical history (not just this event), including any referral diagnostics.
- **Phone interview** about B6 diet and environmental exposures
  - Please confirm permission to contact the owner.
  - The interview generally lasts 30 minutes.

I attached a copy of our Vet-LIRN network procedures. The procedures describe how Vet-LIRN operates and how veterinarians help with our case investigations.
Please respond to this email so that we can initiate our investigation.

Thank you kindly, especially for submitting multiple cases,
Dr. Reimschuessel

Renate Reimschuessel V.M.D. Ph.D.
Director: Vet-LIRN
(Veterinary Laboratory Investigation and Response Network)
Center For Veterinary Medicine, FDA,
8401 Muirkirk Road, Laurel, MD 20708
Phone 1-240-402-5404 Fax 301-210-4685
EMAIL: renate.reimschuessel@fda.hhs.gov

Vet-LIRN
http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm

Phish-Pharm
http://www.fda.gov/AnimalVeterinary/ScienceResearch/ToolsResources/Phish-Pharm/default.htm

Aquaculture
http://www.fda.gov/AnimalVeterinary/ScienceResearch/ResearchAreas/ucm130892.htm

DOCUMENT PRODUCED IN NATIVE

DOCUMENT PRODUCED IN NATIVE

Follow-up Case Information Uniform Data Entry Form
Vet-LIRN

Date (mm/dd/yy): Nov 29, 2018

EON/CC Number: 355,590

PATIENT INFORMATION

Pet Name: B6

(•) Dog ( ) Cat

Breed: White Shepherd

Age in years (if < 6 months, put 0.5): 6

Gender:

( ) M (•) MN ( ) F ( ) FS

This form serves as a Uniform Data Entry Form to capture additional case specific information not clear from the Consumer Complaint or Medical Records in a standardized manner. Because each follow-up interview made with owners features questions tailored specifically to the case, each box of information contained in this Uniform Data Entry Form may not be completed.

HISTORY-Additional Comments from Owner

Owner's Description of What Happened: small hole in heart-discovered 4-5 yr ago; panting harder/coughing?-to rDVM, referred to Tufts-tx; may have been PD but may have been associated w/ Rx; PU after Rx;

Any Health Problems Prior to the Event (e.g. allergies, surgeries): B6 other had blown out as well but not fix B6

Sensitive GI tract (e.g. stomach upset when switching foods, eats a lot of grass) ☐ Yes

Changes to the pet's diet prior to illness ☐ Yes

Date Diet Change:

CLINICAL INFORMATION--Additional Comments from Owner on What Happened

Appetite ☐ Increased ☐ Decreased

Vomiting ☐ Yes

Diarrhea ☐ Yes

Duration of Diarrhea (days):

Blood in Feces ☐ Fresh,Red ☐ Coffee Ground ☐ Black,Tarry

Water Consumption ☐ Increased ☐ Decreased

Urination ☐ Increased ☐ Decreased

Lethargy ☐ Yes

Other: hard panting/coughing?

MEDICATIONS-Taken Prior to the Event and Mentioned by Owner

List medications mentioned by owner (e.g. NSAIDs, steroids, heartworm/flea prevention, antibiotics, etc.): should've been on Simparica

List probiotics, vitamins, or supplements mentioned by owner:

Continued other side

Follow-up Case Information Uniform Data Entry Form
Vet-LIRN

EON/CC Number: 3,559,590

Owner: B6

Pet's Name: B6

DIET-Any other foods the owner mentions were given to the animal during this period. (check all that apply)

☒ Commercial Dry — Product Use as Part of Diet: ☐ Primary ☐ Secondary ☐ Occasional

List Product Label Name: 4Health Grain Free Large Breed Adult Formula-first fed ~5 years ago, possibly 7 years ago, use horse feed scoop and filled bowls in evening (big bowl-4-5 cups, lasted 24 hours and sometimes owner

☐ Commercial Wet-Canned — Product Use as Part of Diet: ☐ Primary ☐ Secondary ☐ Occasional

List Product Label Name: Canned food-couple times/week; Blue Wilderness

☐ Commercial Wet-Pouch — Product Use as Part of Diet: ☐ Primary ☐ Secondary ☐ Occasional

List Product Label Name:

☐ Commercial-Raw — Product Use as Part of Diet: ☐ Primary ☐ Secondary ☐ Occasional

List Product Label Name:

☐ Homemade-Raw — Product Use as Part of Diet: ☐ Primary ☐ Secondary ☐ Occasional

Describe Product Type:

☐ Homemade-Cooked — Product Use as Part of Diet: ☐ Primary ☐ Secondary ☐ Occasional

Describe Product Type:

☒ Table Scraps/Human Food (as an occasional contribution to diet) — Describe Product Type(s): crack an egg in bowls in Summer, banana

☐ Pet Treat Products — Product Use as Part of Diet: ☐ Primary ☐ Secondary ☐ Occasional

☒ Commercial	Product Label Name/Lot:	Biscuits, Dentastix or similar, Block of firewood w/ Wc	Date first fed	
	How Product Administered:		Date last fed	
☒ Rawhides or Pig Ears	Product Label Name/Lot:	sometimes Bully stick, maybe 1 pig ear / year	Date first fed	
	How Product Administered:		Date last fed	
☐ Marrow Bones	Product Label Name/Lot:		Date first fed	
	How Product Administered:		Date last fed	
☐ Chicken Jerky	Product Label Name/Lot:		Date first fed	
	How Product Administered:		Date last fed	
☐ Duck Jerky	Product Label Name/Lot:		Date first fed	
	How Product Administered:		Date last fed	
☐ Sweet Potato Jerky or Treats	Product Label Name/Lot:		Date first fed	
	How Product Administered:		Date last fed	

Continued other side

Follow-up Case Information Uniform Data Entry Form
Vet-LIRN

EON/CC Number: 355,590

Owner: B6 ...

Pet's Name: B6

DIET-*continued*-Any other foods the owner mentions were given to the animal during this period. (check all that apply)

☐ Other Treats

Product Label Name/Lot:

Date first fed

How Product Administered:

Date last fed

ENVIRONMENTAL EXPOSURES-Environmental Exposures Mentioned by the Owner Potentially Affecting the Animal's Overall State of Health Prior to the Event . (check all that apply)

☐ Indoor	☐ Outdoor	☐ Indoor & Outdoor	☐ Carrion	☐ Rodents	☐ Grapes or Raisins	☐ Nuts
☐ Plants	☐ Trash	☐ Hunt	☐ Pet Shows	☐ Sporting Events	☐ Pet Recreation Facilities	
☐ Livestock	☒ Poultry	☐ Reptiles	☐ Pet Birds	☐ Small Mammals	☒ Untreated Surface Water	
☐ Anti-freeze	☐ Mushrooms	☐ Heavy Metals	☒ Ticks	☐ Urban	☐ Suburban	☐ Rural

Comments:

2 other dogs?

inside at night, outside during day, fenced yard (small in B6 grass w/ trees, in B6 mostly wooded, fenced); owners have chickens; may encounter a squirrel or other dogs on a walk; occ to pet-friendly lake or puddle/stream he'd jump in (enjoyed swimming); sometimes sit in garage but not near the owner;

mouse pellets inside cases weren't disturbed; have woods-ticks get bad in summer;

no trauma or hyperthermia (still cool), no radiation or electric shock, no chemo drugs/human Rx/vitamins; owners have a toddler-good about picking things up; no alcohol exposure unless licking window that'd have been cleaned an hour before; no Japanese yew, foxglove, black locust, buttercup, lily of the valley, gossypol exposure;

HOUSEHOLD-Signalment of Additional Animals Given the Product mentioned by the owner.

Animal 1: 2 other dogs got same food- ☐ Reacted

Animal 2: GSD-MC, 13 yr-died in B6 been fighting it a year, back legs weren't working; gradually went downhill the past year ☐ Reacted

Animal 3: Husky- 6 yr-FS-doing fine ☐ Reacted

Comments

Submit

From: Jones, Jennifer L </o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0f6ca12eaa9348959a4cbb1e829af244-Jennifer.Jo>
To: Rotstein, David; Palmer, Lee Anne; Carey, Lauren
Sent: 4/3/2019 1:57:30 PM
Subject: RE: ACANA - Heritage Red Meat Formula Dog Food (Grain-free) B6 - EON-383914

FYI-MRx in PFR show DCM w/ CHF. B6 is submitting reports from Tufts (in leui of Lisa Freeman)
NFA for Vet-LIRN

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421
U.S. FOOD & DRUG ADMINISTRATION

From: PFR Event <pfreventcreation@fda.hhs.gov>
Sent: Monday, April 01, 2019 5:49 PM
To: Cleary, Michael * <Michael.Cleary@fda.hhs.gov>; HQ Pet Food Report Notification <HQPetFoodReportNotification@fda.hhs.gov>; B6
Subject: ACANA - Heritage Red Meat Formula Dog Food (Grain-free) B6 - EON-383914

A PFR Report has been received and PFR Event [EON-383914] has been created in the EON System.

A "PDF" report by name "2065085-report.pdf" is attached to this email notification for your reference. Please note that all documents received in the report are compressed into a zip file by name "2065085-attachments.zip" and is attached to this email notification.

Below is the summary of the report:

EON Key: EON-383914
ICSR #: 2065085
EON Title: PFR Event created for ACANA - Heritage Red Meat Formula Dog Food (Grain-free); 2065085

AE Date	03/15/2019	**Number Fed/Exposed**	2
Best By Date		**Number Reacted**	1
Animal Species	Dog	**Outcome to Date**	Stable
Breed	Shepherd Dog - German		
Age	11.5 Years		
District Involved	PFR-New England DO		

Product information
Individual Case Safety Report Number: 2065085
Product Group: Pet Food
Product Name: ACANA - Heritage Red Meat Formula Dog Food (Grain-free)
Description: 3/15/2019 - Acute onset of difficultly breathing on walk, increased resp rate, wheezing and short of breath. Diagnosed with DCM and CHF

Submission Type: Initial
Report Type: Adverse Event (a symptom, reaction or disease associated with the product)
Outcome of reaction/event at the time of last observation: Stable
Number of Animals Treated With Product: 2
Number of Animals Reacted With Product: 1

Product Name	Lot Number or ID	Best By Date
ACANA - Heritage Red Meat Formula Dog Food (Grain-free)		

Sender information

B6

USA

Owner information

B6

To view this PFR Event, please click the link below:
https://eon.fda.gov/eon//browse/EON-383914

To view the PFR Event Report, please click the link below:
https://eon.fda.gov/eon//EventCustomDetailsAction!viewReport.jspa?decorator=none&e=0&issueType=12&issueId=401042

==========

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DOCUMENT PRODUCED IN NATIVE

From: Jones, Jennifer L </o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0f6ca12eaa9348959a4cbb1e829af244-Jennifer.Jo>
To: Rotstein, David; Glover, Mark; Palmer, Lee Anne; Queen, Jackie L; Carey, Lauren
CC: Ceric, Olgica; Nemser, Sarah; 'Reimschuessel, Renate (Renate.Reimschuessel@fda.hhs.gov)'
Sent: 1/23/2018 6:24:22 PM
Subject: RE: California Natural and Zignature- Kangaroo Diets and DCM EON-345833-345835-345831-345822
Attachments: DeLuca-2015-Taurine-metabolism.pdf; EON-345822-B6-MRx 1.pdf; EON-345822-B6-MRx 2.pdf; EON-345831-B6-MRx 1.pdf; EON-345831-B6-MRx 2.pdf; EON-345833-B6-MRx.pdf; EON-345835-B6-MRx 1.pdf; EON-345835-B6-MRx 2.pdf; EON-Multi-B6-case summary-1.23.2018.doc; EON-Multi-B6-DCM-1.23.2018.xlsx; Listserve on kangaroo and lentil diets.pdf

B5, B6

MRx summaries attached.
The Message Board is worth reading-start on the last page. Good article (DeLuca et al) with Tau biosynthesis diagram (below) attached.

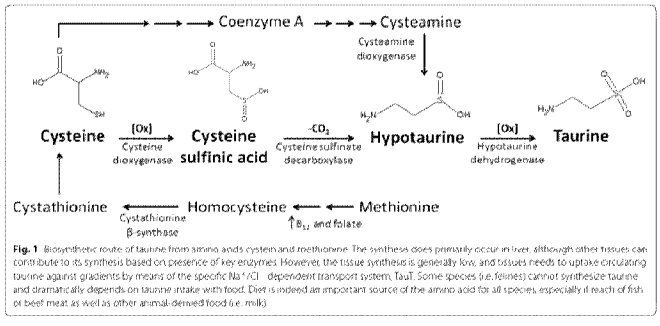

Fig. 1 Biosynthetic route of taurine from amino acids cysteine and methionine. The synthesis does primarily occur in liver, although other tissues can contribute to its synthesis based on presence of key enzymes. However, the tissue synthesis is generally low, and tissues needs to uptake circulating taurine against gradients by means of the specific Na^+/Cl^- dependent transport system, TauT. Some species (i.e. felines) cannot synthesize taurine and dramatically depends on taurine intake with food. Diet is indeed an important source of the amino acid for all species, especially if reach of fish or beef meat as well as other animal-derived food (i.e. milk).

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421
U.S. FOOD & DRUG ADMINISTRATION

From: Rotstein, David
Sent: Tuesday, January 23, 2018 7:02 AM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>; Reimschuessel, Renate <Renate.Reimschuessel@fda.hhs.gov>; Glover, Mark <Mark.Glover@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Queen, Jackie L <Jackie.Queen@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>
Subject: RE: California Natural and Zignature- Kangaroo Diets and DCM EON-345833-345835-345831-345822

Thanks---that's what I figured!

From: Jones, Jennifer L
Sent: Tuesday, January 23, 2018 7:01 AM
To: Rotstein, David <David.Rotstein@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>; Reimschuessel, Renate <Renate.Reimschuessel@fda.hhs.gov>; Glover, Mark <Mark.Glover@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Queen, Jackie L <Jackie.Queen@fda.hhs.gov>; Carey,

Lauren <Lauren.Carey@fda.hhs.gov>
Subject: RE: California Natural and Zignature- Kangaroo Diets and DCM EON-345833-345835-345831-345822

I wasn't-However, I bet it's related to our contact from NCSU. She had a cardiologist friend in **B6** with a few cases. We can get MRx, to start!

Jennifer Jones, DVM
Veterinary Medical Officer
Tel: 240-402-5421

U.S. FOOD & DRUG ADMINISTRATION

From: Rotstein, David
Sent: Monday, January 22, 2018 10:06 PM
To: Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>; Reimschuessel, Renate <Renate.Reimschuessel@fda.hhs.gov>; Glover, Mark <Mark.Glover@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Queen, Jackie L <Jackie.Queen@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>
Cc: Rotstein, David <David.Rotstein@fda.hhs.gov>
Subject: California Natural and Zignature- Kangaroo Diets and DCM EON-345833-345835-345831-345822

Not sure if you were expecting these at Vet-LIRN

De Luca *et al. J Transl Med (2015) 13:243*
DOI 10.1186/s12967-015-0610-1

JOURNAL OF TRANSLATIONAL MEDICINE

REVIEW Open Access

Taurine: the appeal of a safe amino acid for skeletal muscle disorders

Annamaria De Luca*, Sabata Pierno and Diana Conte Camerino

Abstract

Taurine is a natural amino acid present as free form in many mammalian tissues and in particular in skeletal muscle. Taurine exerts many physiological functions, including membrane stabilization, osmoregulation and cytoprotective effects, antioxidant and anti-inflammatory actions as well as modulation of intracellular calcium concentration and ion channel function. In addition taurine may control muscle metabolism and gene expression, through yet unclear mechanisms. This review summarizes the effects of taurine on specific muscle targets and pathways as well as its therapeutic potential to restore skeletal muscle function and performance in various pathological conditions. Evidences support the link between alteration of intracellular taurine level in skeletal muscle and different pathophysiological conditions, such as disuse-induced muscle atrophy, muscular dystrophy and/or senescence, reinforcing the interest towards its exogenous supplementation. In addition, taurine treatment can be beneficial to reduce sarcolemmal hyper-excitability in myotonia-related syndromes. Although further studies are necessary to fill the gaps between animals and humans, the benefit of the amino acid appears to be due to its multiple actions on cellular functions while toxicity seems relatively low. Human clinical trials using taurine in various pathologies such as diabetes, cardiovascular and neurological disorders have been performed and may represent a guide-line for designing specific studies in patients of neuromuscular diseases.

Keywords: Taurine skeletal muscle, Inherited muscle disorders, Disuse muscle atrophy, Development and aging, Skeletal muscle performance

Background

Taurine (2-aminoethane-sulfonic acid) is a sulfur-containing amino acid which is not used for protein synthesis and is therefore the most abundant free amino acid in mammalian tissues, with the exception of human liver in which aspartate is the most abundant one [1, 2]. The intracellular concentration of taurine ranges between 5 and 20 μmol/g wet weight in many tissues, especially in excitable ones, such as brain, heart and skeletal muscle [1, 3, 4]. Endogenous synthesis occurs in the liver via the cysteine sulfinic acid pathway. The metabolic reaction consists in a first oxidation of the sulfhydryl group of cysteine to cysteine sulfinic acid by the enzyme cysteine dioxygenase. Cysteine sulfinic acid is then decarboxylated to hypotaurine by the cystyeine sulfinate decarboxylase. Taurine is obtained by a yet unclear spontaneous or enzymatic oxidation (by hypotaurine dehydrogenase) of hypotaurine (Fig. 1). The endogenous synthesis of taurine is highly variable between individuals also in relation to nutritional state, to the amount of protein intake and to cysteine availability [1, 5]. In turn the availability of cysteine is highly dependent on the metabolic equilibrium between homocysteine and methionine, via folic acid, vitamin B12 and the efficiency of the enzyme methyltetrahydrofolate reductase. In addition, a certain amount of taurine has to be introduced with food, mostly in carnivores and, to a minor extent, in omnivores [1]. The importance of the two sources vary quite a lot between species, with some, like felines and foxes, being highly dependent on diet acquisition of taurine, as they are unable to synthesize it. These species are also particularly susceptible to deficient states, developing severe pathophysiological conditions, such as dilated cardiomyopathy, retinal degeneration and reproduction defects

*Correspondence: annamaria.deluca@uniba.it
Sezione di Farmacologia, Dipartimento di Farmacia-Scienze del Farmaco, Università degli Studi di Bari "Aldo Moro", Bari, Italy

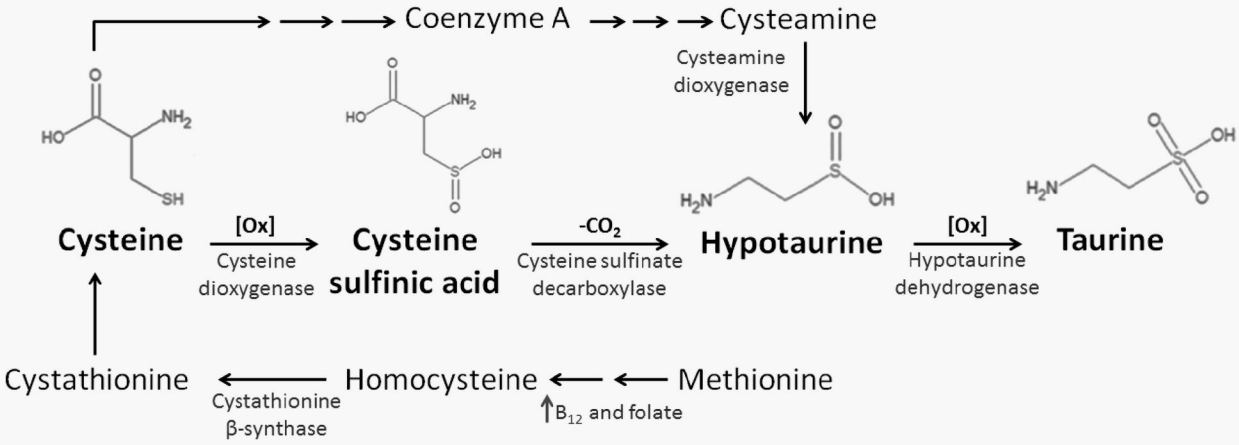

Fig. 1 Biosynthetic route of taurine from amino acids cystein and methionine. The synthesis does primarily occur in liver, although other tissues can contribute to its synthesis based on presence of key enzymes. However, the tissue synthesis is generally low, and tissues needs to uptake circulating taurine against gradients by means of the specific Na^+/Cl^- dependent transport system, TauT. Some species (i.e. felines) cannot synthesize taurine and dramatically depends on taurine intake with food. Diet is indeed an important source of the amino acid for all species, especially if reach of fish or beef meat as well as other animal-derived food (i.e. milk).

[3, 6]. These evidences first outlined the key role of taurine for mammalian tissue functions and helped to better understand the link between tissue distress in retaining proper taurine concentration and various pathophysiological conditions.

In fact, even in species able to synthesize taurine, the tissue-specific synthesis is relatively low, with liver being the main source according to the higher expression of enzymes as cysteine dioxygenase. Importantly, the activity of this latter enzyme strictly depends upon cysteine availability, so that the exact amount of taurine being endogenously synthesized is difficult to predict [7]. However, the high intracellular concentration is guaranteed by the presence of a specific active transporter that concentrates taurine inside the cells against gradients. The taurine transporter (TauT; encoded by the SLC6A6 gene) is a sodium and chloride ion-dependent transporter ubiquitously expressed in mammalian tissues. The concentration of taurine is 100-fold less in the plasma (20–100 μM) than in the tissues, suggesting that it is indeed required for modulating key cellular functions. Due to the high tissue concentration, taurine also works as an osmolyte. Its cellular efflux via volume-dependent or volume-independent pathways works to osmotically balance the excessive production of metabolic by-products. Both uptake systems and efflux pathways are tightly regulated at transcriptional and post-transcriptional level, leading to an accurate control of taurine intracellular levels [8].

Since its discovery in ox bile in 1827, several physiological functions have been described for the amino acid, ranging from the classical role of conjugating agent for bile acids, to wider actions as osmotic pressure regulator, modulator of calcium homeostasis and signaling and, more recently, as an endogenous anti-oxidant and anti-inflammatory compound in various tissues. The mechanism by which taurine exerts all these different functions is still unclear. Some of the taurine actions in central nervous system (CNS), seem to occur via specific binding sites or receptors, i.e. in thalamus taurine modulates neuronal firing via activation of extra-synaptic gamma-amino butyric acid (GABA) receptor isoforms α4β2δ with a greater affinity than GABA [9–12]. Such high affinity binding sites have not been evidenced in other tissues.

Skeletal muscle is one of the tissues able to concentrate the largest amount of body's taurine, via the TauT activity. Pioneer studies of Ryan Huxtable anticipated that the high taurine level is needed to maintain an appropriate calcium homeostasis, likely by ensuring a correct calcium re-uptake by the sarcoplasmic reticulum [13]. Similar actions were also described in heart, with taurine exerting complex modulation of calcium homeostasis in relation to external concentration of the cation with beneficial effects in contrasting arrhythmias or heart failure [1, 3, 4].

Transgenic mice lacking TauT gene have been generated by two separate groups [6, 14–16]. In line with a key role of taurine for maintaining proper physiological functions, the drastic reduction in content consequent to TauT deletion is associated to a variety of disorders in various tissues, such as eye, kidney, heart, nociceptive system and skeletal muscle [14–17]. These conditions resemble those occurring when taurine tissue content is

altered by pathophysiological states or by inhibitors of the taurine transporter. In spite the pre-clinical research has disclosed many conditions in which taurine supplementation may be beneficial, the therapeutic use of taurine is very limited. Taurine is commonly known for its claimed effects as energizer and anti-fatigue compound and it is present in many energy soft drinks as well as in supplement cocktails for athletes. The toxicity of taurine in this context is considered relatively low with respect to other active ingredients; actually it may also be protective against cardiovascular action of caffeine [18]. Such a protection may again result from multiple taurine actions, i.e. an antihypertensive effect via vasodilatation (by reducing adrenergic and angiotensin II actions as well as calcium-induced vasospasm) along with a reduced risk of cardiac arrhythmias via modulation of ion channels and ionic homeostasis [18]. However a certain caution is important especially when taurine is used in children and/or in association with drugs, alchool or other food supplements [19–23]. Apart for its nutraceutical role, taurine may exert clear pharmacological actions by modulating signaling pathways and targets or via restoration of its altered tissue levels. No systematic toxicity studies have been performed to assess the toxicological parameters for taurine; however human trials have used taurine up to 10 g/daily without overt signs of toxicity. This may also depend on the direct relationship between taurine plasma level and its excretion rate by the kidney [19].

An extensive revision of all the actions of taurine in various tissues and the wide potential usefulness of its supplementation is out of the scope of this review. However, a general overview is provided in Fig. 2. As far as inherited or acquired pathophysiological conditions of skeletal muscle are concerned, the pre-clinical findings allow to distinguish effects related to exogenous pharmacological action of taurine on rather specific targets, such as in myotonic syndromes, to conditions that may be accompanied by changes in intercellular taurine content or change in calcium homeostasis, in which a taurine supplementation may be helpful to restore altered levels.

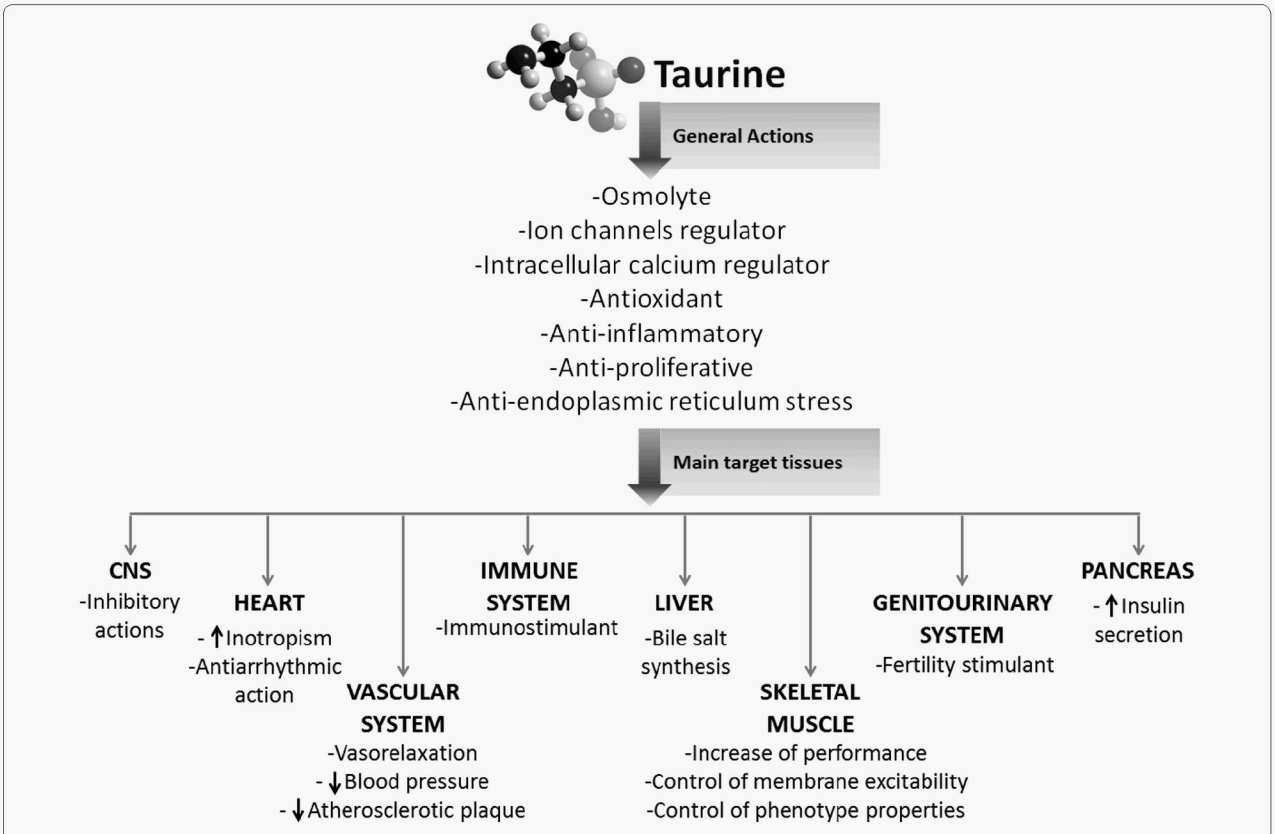

Fig. 2 Taurine plays many and different physiological roles in various tissues. Some taurine actions, as the inhibitory effect at CNS, seem to be mediated by a receptor mechanism, while the effects on other tissues and systems occur via less defined mechanisms of action. Accordingly, the figure also briefly summarizes the main taurine effects ranging from control of calcium handling mechanism and excitation–contraction coupling in the heart, the ability to control immune reaction and inflammation, via inhibition of NF-kB as well as the main role of taurine in conjugating bile salts. Virtually all tissues are sensitive to taurine action with described effect of taurine on visual function (not shown), fertility, insulin release etc. The reported scheme is not supposed to be exhaustive of all taurine effects and only serves as general overview.

The present review is aimed at providing the state-of-art of taurine research in skeletal muscle, with particular attention to its potential therapeutic application as orphan drug in inherited rare muscle disorders, as well as in pathophysiological conditions such as aging, malnutrition and/or muscle disuse.

Skeletal muscle ion channels as specific targets of taurine: the potential action of taurine as anti-myotonic drug

Taurine and skeletal muscle chloride channels ClC-1

In CNS, taurine has been long claimed to act as an "inhibitory" amino acid and neurotransmitter [1]. Neuronal synthesis of taurine and metabotropic taurine receptors have been described in specific areas of CNS, where taurine acts in a glycine or GABA-like manner, by enhancing hyperpolarizing chloride-mediated conductance in nervous cells [9, 11, 12]. Pre-clinical evidences were provided of a beneficial effect of taurine in controlling/preventing seizure discharges and neurotoxicity [1, 12, 24]. The ability of taurine to act as inhibitory amino acid raised attention to its possible effect as potential membrane stabilizer in skeletal muscle. We investigated about the actions of the amino acid on voltage-gated chloride channels CLC-1 that account for the macroscopic chloride conductance (gCl) of skeletal muscle. Resting gCl accounts for about 70–90% to the total membrane conductance of sarcolemma and plays a pivotal role in maintaining the sarcolemmal electrical stability by shunting the depolarization-driven potassium accumulation in transverse tubules. Thus the large gCl allows repolarization and muscle relaxation.

Loss-of-function mutations of CLC-1 are responsible of myotonic syndromes with either autosomal dominant (Thomsen disease) or recessive pattern of inheritance (Becker's Myotonia Congenita). The resulting decrease of gCl is responsible for the pathological hyperexcitability and for the delayed relaxation, spasms and stiffness typical of the disease in both patients and myotonic animals [25–27].

Our research has shown that taurine, acutely applied in vitro, exerts a concentration-dependent increase of gCl in rat extensor digitorum longus (EDL) myofibers, and in parallel reduces membrane excitability [28, 29]. The effective concentrations are in the millimolar range, likely in relation to the high intracellular level of the amino acid [28, 29]. A pre-clinical evaluation of the potential anti-myotonic activity of taurine has been performed. We found that taurine does not antagonize the myotonic discharges in rats made myotonic by administration of anthracene-9-carboxylic acid, a direct chloride channel blocker, nor does it restore gCl lowered in vitro by the same agent. However, when rats are made myotonic by a chronic exposure to 20,25 diazacholesterol, which reduces gCl indirectly by modifying lipid membrane composition, taurine antagonizes the electromyographic signs of myotonia if administered in vivo, while its acute in vitro application contrasts both the reduced gCl and the high frequency firing of single myofibers [30]. These results suggested that taurine can contrast myotonia if chloride channels are available for a direct modulation, implying its direct action at channel level or on a site nearby. A series of taurine analogues were tested on gCl of rat EDL myofibers to investigate the structure–activity relationship (SAR) between taurine and chloride channels. The results provided a pharmacological evidence of the presence of a specific low-affinity taurine binding site able to modulate chloride channel function and/or kinetic [31]. In particular, an increased distance between the two charged heads of taurine and/or a more distributed positive charge for the replacement of the amino group with aza-cyclo moieties lead to a decreased potency in enhancing gCl [31]. The direct action of taurine on skeletal muscle chloride channel was further confirmed by two microelectrode voltage-clamp recordings of chloride currents sustained by human ClC-1 channel heterologously expressed in Xenopous oocytes. In these conditions, the in vitro application of 20 mM taurine enhanced by 100% the chloride currents and shifted channel activation toward more negative potentials, an effect that likely accounts for the increase in resting gCl observed in native fibers [32–34]. This direct modulation adds to other possible homeostatic and modulatory roles that the high intracellular taurine has on chloride channels. However, as anticipated, the acute modulation of gCl may require fully or partly functional chloride channels, questioning about the real efficacy of taurine in ClC-1 related myotonic syndromes, especially for those mutations that seriously affect channel expression and protein level. Taurine has been tested in patients with myotonic dystrophy with encouraging results. In particular acute parenteral administrations of taurine allowed to reduce membrane excitability evaluated in relation to potassium plasma concentration after potassium-enriched infusion, suggesting again an action on membrane ionic conductance. Accordingly, a double-blind oral administration of taurine led to a long-term control of myotonic symptoms estimated as reduction of electromyographic (EMG) discharges and potassium induced-hyperexcitability [35–37]. Even taking into account the possible bias deriving from these small sized trials, the effects of taurine in myotonic dystrophy patients suggest alternative modality for decreasing membrane excitability. In fact, myotonic dystrophy type 1 (DM1) or Steinardt syndrome, is caused by expansion of a CTG trinucleotide repeat in the non-coding region of DM protein kinase with abnormalities

in mRNA metabolism and alternative splicing of certain genes. In DM1 patients, the abnormal inclusion of alternative exons 6B and/or 7A and retention of intron 2 of CLC-1 channel gene (*CLCN1)* gene have been observed. These aberrant-splicing, which may also occur in myotonic dystrophy type 2 (DM2) patients, leads to premature termination codons, with a consistent decrease of the mRNA of *CLCN1*, of ClC-1 protein and consequently of gCl [38, 39]. Therefore, the possible modulatory action of taurine on other skeletal muscle ion channels has to be taken into account.

Taurine and Nav1.4 voltage gated sodium channels

It is feasible to hypothesize a modulation by taurine of the skeletal muscle isoform of voltage-gated sodium channel (Nav1.4), involved in the generation and propagation of action potential and main target of symptomatic antimyotonic drugs [37, 40]. The effect of taurine on sodium channels of native muscle fibers has been investigated in our laboratories by cell-attached patch clamp recordings. Taurine has a dual effect. In particular taurine enhances the sodium transients elicited by depolarizing test pulses close to the threshold for channel activation (test pulse to −70/−50 mV), an effect that is likely related to the observed shift of the activation curve towards more negative potentials. However, taurine reduces sodium currents at more depolarized test pulse potentials, with a 50% inhibition of the maximal peak sodium current observed at 10 mM taurine. In parallel, a left-shift of the steady-state inactivation curve has been observed, indicating the ability of taurine to stabilize the blocked channels in the inactivated state [34, 41 Desaphy and Conte Camerino, unpublished observation]. This peculiar effect of taurine on Nav1.4 channel is similar to what has been observed on cardiac sodium currents [42, 43] and underlines a complex action of the amino acid on sodium channel gating and kinetic. Our extensive structure–activity relationship studies of inhibitors of Nav1.4 channel allow to predict that the anesthetic-like action of taurine is mediated by the amino group, a main pharmacophore moiety in sodium channel blockers [44–47]. The dual ability of taurine to open chloride channels and to block sodium channels envisages a greater therapeutic action of the amino acid in myotonic states related to gain-of-function mutations of sodium channels, such as Sodium Channel Myotonia and Paramyotonia Congenita. The verification that taurine is able to compensate mutation-related biophysical alterations of Nav1.4 channels will be helpful at this regard, and is part of future projects of our laboratory. For the moment, the action of taurine on sodium channels can account for the antimyotonic effect in conditions where chloride channels are defective or dysfunctional [35, 36]. In line with this, the mechanism of taurine action on Nav1.4 sodium channels deserves to be further investigated since it may better support its pharmacological potential and its clinical use in hyperexcitability muscle disorders (Table 1).

Role of proper taurine intramuscular level for excitation–contraction coupling and muscle performance

The ability of skeletal muscle to concentrate taurine against gradient pushed toward a better understanding of its physiological role. Adult rats were chronically treated with guanidinoethane sulfonate (GES), an inhibitor of taurine transporter (TauT) to induce a reduction of taurine content in skeletal muscle. We found that a 50% reduction of taurine in EDL muscle leads to a marked decrease in gCl, and to a parallel enhancement of sarcolemmal excitability, disclosing the ability of taurine level to exert a physiological control on chloride channel function and sarcolemmal stability [48]. The mechanism underling this effect is not clear yet, but we cannot rule out the ability of taurine to modulate ClC-1 channel function via a fine-tuning of a calcium-dependent phosphorylation-signaling pathway, as discussed below. In line with the described ability of taurine to control calcium homeostasis in both skeletal muscle and cardiac tissue [1, 4], we found a marked alteration of mechanical threshold, i.e. the voltage at which muscle fiber contracts in response to depolarizing voltage steps, in taurine-depleted EDL myofibers. Mechanical threshold depends on the kinetic of calcium release from and reuptake by sarcoplasmic reticulum, also in relation to basal cytosolic calcium concentrations. Taurine depleted EDL muscle fibers contract at more negative potentials with respect to normal ones, implying an impact of GES treatment on calcium handling [48, 49]. Both the decrease in gCl and the shift of mechanical threshold toward negative potentials were rapidly reverted by in vitro application of millimolar concentration of taurine. Actually, depleted muscles showed a higher than normal sensitivity to exogenous taurine with respect to normal ones [48], further corroborating the link between the observed alterations and the taurine level. The contractile properties and fatigability of EDL muscles depleted of taurine by a GES treatment were investigated by Bakker's group. It was found that the treatment with GES decreases muscle taurine levels to <40% of controls and decreases the peak twitch force of EDL muscles by 20%. Also, GES-treated muscles develop a lower force in force–frequency relationship and show a slower time to fatigue, likely in relation to the lower metabolic demands of the weaker muscles [50]. Primary information about the long-term effect of taurine in skeletal muscle and, consequently, of potential usefulness of its exogenous administration

Table 1 Involvement and therapeutic potential of taurine in physio-pathological conditions and diseases of skeletal muscle

Condition	Change in Taurine content / TauT	Pathogenetic mechanisms related to changes in taurine content	General symptoms	Taurine targets	Therapeutic Potential of Taurine
Post-natal development	Age-dependent increase in TauT expression and intracellular content	Delayed development and delayed acquisition of specific phenotypic properties; metabolic dysfunction	Specie-specific (due to different sensitivity to taurine deficiency)	Mitochondria; ion channels; calcium homeostasis and calcium dependent gene expression	Taurine supplementation in formula for pre-term born infants; to ensure a proper skeletal muscle phenotype differentiation
Aging	Decrease in Taurine content; no information on TauT expression	Metabolic distress; calcium dependent dysfunction; reduced regenerating ability; reduced activity of free-oxygen radicals scavengers	Sarcopenia; atrophy, weakness and fatigue degeneration, altered excitation–contraction coupling, impaired performance	Ion channels; Calcium homeostasis; oxidative stress and atrophy	To counteract the decrease in taurine content and the consequent reduction in chloride channel function and the alteration in calcium ion homeostasis; to ameliorate performance and muscle strength
Ischemia and reperfusion injury	Decrease due to a compensatory taurine efflux	Insufficient vaso-dilation in relation to muscle work; metabolic distress; oxidative stress	Hyperkaliemia, muscle dysfunction; ROS-induced inflammation and damage	Metabolic-sensitive channels; mitochondria	To counteract hyper-kaliemia by inhibiting K_{ATP} and KCa^{2+} channels; to prevent ischemia-induced taurine loss
Myotonic syndromes and periodic paralyses	Unknown	Primary inherited channelopathies due to loss-of function mutations of ClC-1 chloride channel or gain-of-function mutations of Nav1.4 sodium channel	Hyperexcitability and impaired muscle relaxation	ClC-1 chloride channel; Nav1.4 sodium channel	To reduce membrane hyper-excitability through: opening of chloride channel and increase in gCl mediated by both short and long term actions; modulation of generation and propagation of action potential, by blocking sodium channel with a local-anesthetic like mechanism
Disuse	Slow-to-fast decrease in taurine content; no change in TauT expression	Myofiber phenotype transition in postural muscle; atrophy	Atrophy, change in metabolism, slow-to-fast transition; weakness	Ion channel function and expression; calcium homeostasis	To counteract disuse-induced taurine loss; to counteract myofiber transition; potential counteraction of atrophy
Duchenne muscular dystrophy and related myopathies	Change in content related to pathology phase; possible reduction of TauT expression	Alteration of calcium homeostasis; calcium-related degeneration; oxidative stress and inflammation	Progressive muscle degeneration and weakness; muscle fiber loss and fibrosis; sarcolemmal instability; altered calcium homeostasis; inflammation and oxidative stress	Chloride channel and voltage-insensitive calcium permeable channels (Leak/TRP-like); SERCA; mitochondria	To ameliorate muscle performance; to counteract taurine loss and to modulate calcium availability for contraction; to counteract contraction-induced ischemia. To contrast degeneration-induced decrease in gCl; adjuvant therapy in combination with glucocorticoids

The table summarizes the main role of taurine in various conditions of skeletal muscle, indicating evidences in relation to changes in tissue content and potential site of taurine action. Please refer to text for more detailed information and specific references.

TauT taurine transport system, *SERCA* sarco/endoplasmatic reticulum calcium ATPasi, *gCl* macroscopic chloride conductance, *TRP* transient receptor potential channels, *ROS* reactive oxygen species, *KATP* ATP-dependent potassium channels, *KCa* calcium activated potassium channels.

derives from studies on mice in which the TauT was genetically knocked out [6, 14–16]. TauT knockout mice ($TauT^{-/-}$) show more than 90% decrease in taurine content in both muscle and heart and are characterized by a marked decrease in exercise performance in exhaustive training models. Although the force of isolated muscle has not been measured in these $TauT^{-/-}$ mice, clear abnormalities of muscle structure have been found, including signs of atrophy and muscle necrosis. Additionally, the muscles of $TauT^{-/-}$ mice have a shift of metabolism toward the glycolytic pathway, especially in condition of exercise; this has been related to a dysfunction in mitochondrial function and in fatty acid oxidative pathways [51]. In parallel, taurine deficiency leads to cardiomyopathy characterized by remodeling of ventricular cardiomyocytes, ultrastructural damages of myofilament and mitochondria, and overexpression of markers of heart failure, such as atrial natriuretic peptide, brain natriuretic peptide and beta-myosin heavy chain [15, 16].

It is therefore evident that taurine is essential to maintain muscle performance and excitation–contraction coupling; however the mechanism for these actions is still unclear. An in vitro study of Berg and Bakker clearly demonstrated the ability of taurine to increase the accumulation of calcium into sarcoplasmic reticulum (SR) in isolated skinned myofibers by 35%, an effect that accounts for the greater depolarization-induced contraction of fiber exposed to 20 mM taurine. This in spite taurine slightly reduces the sensitivity of contractile apparatus to calcium [52]. Interestingly, a recent study demonstrated that a prolonged exposure to 10–20 mM taurine increases the rate of calcium uptake in both type I and type II human myofibers; an action within the SR lumen has been proposed. An increase in contractile sensitivity to calcium was also observed but exclusively in type I fibers [53]. These results reinforce the original data of Huxtlable and Bressler about the ability of taurine to stimulate calcium uptake by vesicles of SR [13]. Recent insight into the role of taurine in skeletal muscle has been obtained by the group of Hayes, who supplemented rats with taurine and evaluated the outcome on various functional parameters [54]. Taurine supplementation significantly increases the amino acid content in skeletal muscle, without any adaptive change in TauT activity; in parallel an increase in force and a greater resistance and recovery after fatigue have been observed. These changes were paralleled by an increase in calsequestrin1, the calcium binding protein that works to maintain high amounts of calcium in the cysterna of SR. This suggests that taurine supplemented muscle can store a greater quantity of calcium with a consequent greater calcium availability for contraction. However, the involvement of sarco/endoplasmic reticulum calcium-ATPase (SERCA) remains to be better clarified. A decrease in markers of oxidative stress was also found, indicating that taurine may help to control activity-related oxidative stress [48]. In support to this view, a recent report by Silva et al. showed that a daily treatment of rats with 300 mg/kg taurine for 2 weeks protects muscles against in vivo eccentric exercise damage, such as downhill running [55]. In particular taurine reduced protein carbonylation or oxidized thiols, without increasing the expression of endogenous anti-oxidant pathways, such as superoxide dismutase or catalase [55]. Sugiura et al. similarly found that taurine administration before strenuous exercise reduces muscle DNA damage likely via down-regulation of inducible nitric oxide synthase (iNOS) and consequent reduction of nitrosative inflammation [56]. The protective effects of taurine supplementation are due to a long term modulatory effect, likely in relation to its muscle uptake and intracellular levels. In fact acute in vitro application of physiological concentrations of taurine to isolated mouse soleus muscle, does not increase muscle contractile performance in term of force, fatigue resistance and recovery and does not exert any synergistic action when associated with caffeine [57]. Despite the authors suggesting a lack of ergogenic benefit by acute taurine, it is important to underline that slow twitch soleus muscle is characterized by high intracellular taurine content [58, 59], predicting its lower dependency on extracellular concentrations. Accordingly, we have shown that a chronic treatment with taurine to dystrophic mice leads to a minor increase of its intracellular content in soleus muscle than in fast twitch muscles [59].

Although taurine supplementation enhances exercise performance, its efflux during exercise and/or ischemia, with consequent decrease in tissue concentration, can also occur [60, 61]. Whether the loss of taurine is a marker of tissue damage or rather a cytoprotective mechanism against ischemic insult, is still matter of debate [60, 62, 63]. The protective effect of taurine efflux in the above conditions can be related to the need to osmotically balance, along with water movement, the increase of by-products of metabolism in the myofibers [1, 14]. However a role in the mechanism to contrast fatigue can be envisaged. In fact, taurine exerts an inhibitory control on channels that couple the metabolic state of the myofiber with membrane excitability, such as the ATP-dependent potassium (KATP) channels and calcium-activated potassium channels [64, 65]. Taurine blocks skeletal muscle KATP channel by binding the channel complex nearby the sulphonylurea receptor [64]. During ischemia–reperfusion injury, the opening of KATP are involved in the cytoprotective effect of the preconditioning mechanisms, by preventing the influx of calcium ions and preserving the ATP

content of the muscle. The efflux of taurine during exercise and/or ischemia may be required to relief a basal inhibitory effect and to enhance the potassium efflux and membrane repolarization via the specific channels activated by ATP depletion and/or intracellular calcium accumulation. This would exert a protective action against exercise-induced fatigue or impairment in muscle performance related to ischemia–reperfusion injury [64, 65]. Accordingly, the depletion of taurine induced by GES in rat skeletal muscle significantly increases the macroscopic resting potassium conductance of about 80% [48].

Intracellular taurine can also be conjugated in mitochondria of extra-hepatic tissues to 5-taurinomethyl uridine that is present in tRNA and modulates the synthesis of mitochondrial proteins. Consequently, the fatigue and the enhanced oxidative stress observed in myopathic states by taurine depletion can also be due to respiratory chain inefficiency [4, 51, 66]. A representative scheme of the taurine actions in striated myofibers is shown in Fig. 3.

Taurine as potential therapeutic muscular agent from birth to elderly

The role of taurine for post-natal development of various organs depends upon the species-specific ability to endogenously synthesize the amino acid. Cats, that critically depend on exogenous taurine intake, develop serious impairments during post-natal development if not fed with taurine. Although less compelling for humans, prematurely born infants are believed to lack the enzymes that convert cystathionine to cysteine, and may, therefore, become taurine-deficient if not breast-fed. In fact taurine is present in mother's milk and evidences are available about potential usefulness of taurine addition in the formula especially for pre-term births [67, 68]. The actual necessity or benefit of this practice has never been rigorously studied, and as such, taurine has yet to be proven to be important during fetal development, perhaps via epigenetic and/or organogenesis related mechanisms. Recent focus has been addressed to the potential benefit of taurine supplementation in mice during gestational period, especially when mothers are exposed to

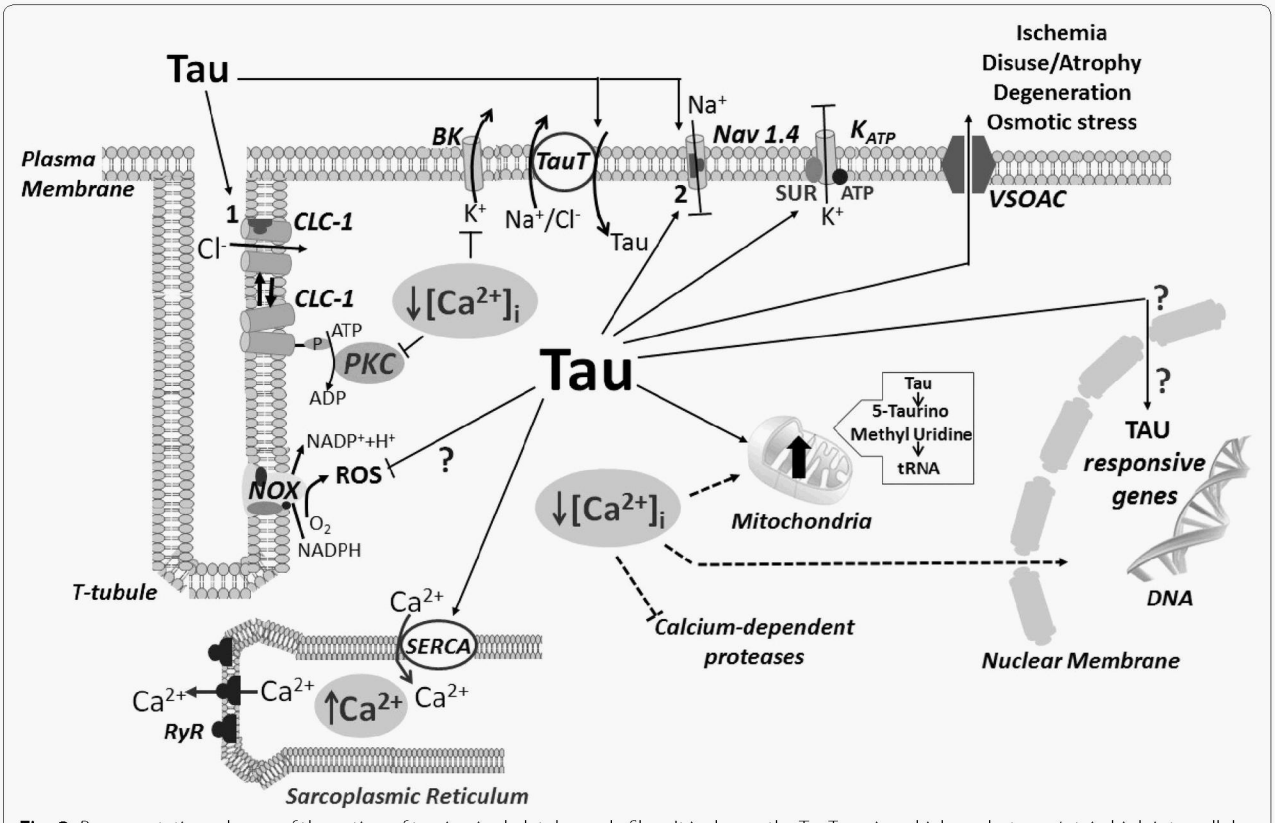

Fig. 3 Representative scheme of the action of taurine in skeletal muscle fiber. It is shown the TauT carrier which works to maintain high intracellular taurine level, along with the actions that taurine exerts on membrane channels, sarcoplasmic reticulum, mitocondria and possibly gene expression. Putative binding sites for taurine are shown (1) on ClC-1 channel and (2) as local anesthetic drug binding site. *Arrows* indicate a general stimulating action while *dotted lines* are for inhibitory effects or yet undefined pathways. A pathway for taurine efflux under stress conditions (ischemia, osmotic stress, etc.) likely via the volume-sensitive organic anion channel (VSOAC) is also shown.

low-protein diet, a condition mimicking the low weight at birth and related to the risk of developing dysmetabolic states later on [69]. In these conditions taurine protects pancreas by decreasing islet sensitivity to cytokines and shows to have an impact on gene expression and "reprogramming" in various tissues, including skeletal muscle [70–72].

In support of the pivotal role of adequate taurine level for skeletal muscle development, we demonstrated that taurine muscle level increases during the first month of rat post-natal life [73]. This increase matches the acquisition of phenotype-specific contractile properties. In particular in rat fast-twitch EDL muscle it occurs in parallel with the post-natal increase in muscle gCl and of ClC-1 channels expression; i.e. during the acquisition of the mature profile [39, 73–75]. Adult levels are likely to be attained later, since a proton nuclear magnetic resonance (H-NMR) study showed an increase in taurine in different rat skeletal muscles from 6 to 18 weeks of age [76]. Accordingly, an age dependent increase of taurine as well as of other amino acids, has been found in muscle of metabolically healthy children (age range 1–15) with respect to adults [77].

In agreement with an active role of taurine for muscle phenotype acquisition, supplementation of mothers during pregnancy and lactation as well as of new-born rats results in a higher content of the amino acid in skeletal muscle, accompanied by a more rapid development of gCl [73]. Whether such an increase is due to a modulatory action of taurine on ClC-1 channel or to an effect on its gene expression is not known yet. Importantly, a profound alteration in gene expression has been described in liver and skeletal muscle of pups that were exposed prenatally to low protein diet, while the addition of taurine to mothers via drinking water during gestation leads to a marked protection [71, 72]. Focusing on skeletal muscle, the rescuing effect of taurine did occur for genes involved in oxidative phosphorylation and in the tricarboxylic acid cycle that were markedly down-regulated in skeletal muscle by the low protein diet. Importantly, plasma taurine concentration has been suggested to be a marker of fetal well-being and a prerequisite for normal fetal development [78]. In line with the important role of taurine for skeletal muscle development, the TauT expression increases during myogenesis and its gene has consensus site for myocyte enhancing factor 2 (MEF2), being therefore under strict control of myogenic program [79]. Also, taurine has been shown to stimulate myofiber differentiation in vitro [80]. Although the mechanism through which taurine may control gene expression during development is not clear yet, it appears to be a necessary factor in myogenesis, and perhaps in mitochondrial biogenesis, with key role for tissue development (Table 1).

Another condition that may benefit from taurine supplementation is aging. Age-related sarcopenia is accompanied by profound changes in hormonal and metabolic profile of skeletal muscle. An important alteration in the content of various amino acids occurs in human muscle specimen with age, as a result of age-related increase in proteolysis; in parallel a marked decrease in taurine content has been observed [81].

Besides sarcopenia, skeletal muscle of aged rats develops features that are overlapping those observed in taurine depleted muscles, i.e. a marked decrease in gCl and a change in calcium homeostasis with a shift of mechanical threshold towards more negative potentials [82, 83]. We found by high-performance liquid chromatography (HPLC) determination that muscle taurine concentration is in fact significantly decreased in muscle of aged rats; however the levels can be restored to adult values upon the exogenous administration of taurine for 3 months (1 g/kg in drinking water) [84]. Importantly, the taurine administration counteracts the decrease in gCl and the alteration in excitation–contraction coupling of aged rat EDL muscle, supporting the key role of the amino acid in the alterations observed and the potential beneficial role of its supplementation in elderly subjects (Table 1). In the EDL muscle of aged rats supplemented with taurine an almost complete recovery of the pharmacological sensitivity of gCl to either direct and indirect channel modulators, such as the enantiomers of p-chloro-phenoxy propionic acid and the phorbol esters, respectively, was observed. The effect of these latter, along with the amelioration of mechanical threshold observed, discloses the ability of taurine to modulate gCl by reducing the phosphorylation state of the chloride channel brought about by calcium and phospholipid-dependent protein kinase C [83, 84]. This offers a unifying mechanism for physiological taurine action via calcium homeostasis and modulation of calcium-dependent signaling pathways.

In line with the above observations, $TauT^{-/-}$ mice show accelerated senescence, with greater muscular damage and endoplasmic reticulum stress due to accumulation of misfolded proteins. A central role of calcium mishandling has been proposed, along with the interest in maintaining adequate taurine level for contrasting aging-related muscle impairments [85].

Taurine and muscular dystrophy

The alteration of calcium homeostasis is a hallmark of muscles affected by inherited muscular dystrophy, such as in mice with X chromosome-linked muscular dystrophy (mdx), the most widely used model for Duchenne muscular dystrophy (DMD). It is believed that the absence of dystrophin, a protein with a key role for sarcolemmal integrity and mechano-transduction, leads to

sarcolemmal tears and to overactivity of voltage-insensitive cationic channels which enhance passive calcium entry, especially during work load [86–88]. This in turn leads to both the alteration of excitation–contraction coupling and to the activation of degenerative pathways [88, 89]. We have found that the EDL muscles of dystrophic mdx animals undergoing chronic exercise protocols, have features resembling taurine depleted ones, i.e. a reduction of gCl and a negative rheobase voltage for mechanical activation [89, 90]. Dystrophic muscle may have a reduced ability in retaining intracellular taurine; in fact we observed a trend of a lower than normal taurine muscle concentration in parallel with markedly high levels in plasma [89]. Accordingly, other authors found that taurine levels fluctuate in mdx muscles in relation to the disease phase, with compensatory increases being observed after acute degenerative period and glucocorticoid treatment [91, 92]. In this frame, taurine seems to be a useful marker of the dystrophic state of mdx mice when monitored by H1-magnetic resonance spectroscopy both in vivo and ex vivo, although technical problems may still limit the accurate peak resolution for quantitative evaluation [91–95]. In our experiments, the in vitro application of millimolar taurine concentrations fully restored the alteration of mechanical threshold observed in these animals [89]. Interestingly, similar results have been obtained upon chronic taurine treatment in exercised mdx mice. The in vivo treatment also significantly contrasted the decrease in gCl and lead to a significant increase of mouse strength in vivo, due to an interesting anabolic action of the amino acid in the dystrophic animals [90]. As previously mentioned, $TauT^{-/-}$ mice are characterized by a marked 80% decrease in exercise performance and increased fatigability, a feature that is classically observed in the mdx phenotype [6, 14, 90, 96]. The role of taurine in muscular dystrophy is also under study in Hayes' laboratory, where a lower expression of TauT in mdx mouse muscle has been demonstrated, which is not influenced by exogenous taurine administration [97], supporting the difficulty of dystrophic muscle to retain taurine. Exercise protocols may differently modulate intramuscular taurine concentration, ranging from no change to phenotype-dependent decrease, likely in relation to the exercise type; however taurine supplementation can enhance exercise performance [60, 61]. Due to the impaired mechano-transduction of dystrophic myofibers, it would be of interest to evaluate whether the exercise protocol in mdx mice can lead to a further distress in taurine concentration and in TauT expression; this is currently ongoing in our laboratory.

Based on first encouraging results, we tested the possible advantage to combine taurine with α-methylprednisolone, a glucocorticoids currently in use in dystrophic patients [58]. A synergistic action of the two drugs in enhancing mouse strength and in restoring calcium homeostasis was observed, with a normalization of mechanical threshold and a reduction of the overactivity of the cation channels likely involved in abnormal calcium entry [58, 86, 98]. The treatment was also associated with a significant increase in taurine content in fast-twitch limb muscles, suggesting that dystrophic muscle maintains the ability to uptake taurine if adequately supplemented [58]. The synergistic action observed corroborates a potential interest of taurine as adjuvant therapy in steroid-treated patients. This is also supported by the evidence that glucocorticoids exert an inhibitory action of renal taurine re-uptake, then leading to hypotaurinemia, which in turn may have long-term negative effects on cardiovascular function [5].

Importantly, the taurine treatment to mdx mice significantly reduces the high plasma level of lactate dehydrogenase, an index of metabolic distress, and it is worth to underline that a marked increase in plasma lactate actually occurs in $TauT^{-/-}$ mice [6]. Therefore taurine can also play a role in metabolism in dystrophic muscle, similarly to what observed in exercise-challenged $TauT^{-/-}$ mice [51].

Increasing evidences suggest a link between calcium homeostasis, oxidative stress and mitochondrial distress in muscular dystrophy, leading to reconcile all these taurine actions under few main mechanisms, although not fully clear yet [99, 100]. As already mentioned, taurine supplementation contrasts the exercise-induced increase in oxidative markers, without enhancing the level of endogenous anti-oxidant [55]. Other evidences support that the sulfonic amino acid is actually incapable of scavenging the common oxidants, namely, superoxide, hydrogen peroxide and hydroxyl radical, which instead are the main products of enhanced NADPH oxidase activity in dystrophic muscle [99–101]. However, the amino group of taurine can neutralize hypochlorous acid, one of the reactive species generated by myeloperoxidase-halide system in neutrophils [102]. In that reaction, taurine is converted to taurine chloramine, which is less toxic than hypochlorous acid and actually serves as a modulator of the immune system also by interfering with the production of several pro-inflammatory mediators and activation of the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) [102]. In addition, taurine has been proposed to directly activate peroxisome proliferator-activated receptor γ (PPARγ) in epithelial cells, a mechanism that may account for its protective action against inflammation-related diabetic retinopathy progression [103]. In consideration of the involvement of chronic inflammation and NF-kB derived mediators in dystrophic muscle [87,

104, 105], the above immunomodulatory actions of taurine are of value. However, whether the anti-inflammatory and anti-oxidant action contributes to the beneficial effect observed in dystrophic animals is not known yet and the evaluation of biomarkers in samples of taurine treated mdx mice will be useful at this regard. Our preliminary results favor a decrease in superoxide anion formation, measured by dihydroethidium staining, in tibialis anterior muscles of exercised mdx mice treated with taurine (De Luca, personal unpublished observations). An attractive hypothesis, currently under study in our laboratory, is that taurine may contrast the impaired SERCA activity in dystrophic muscle either directly or by reducing the damaging effect brought about by oxidation and/or nitrosylation [13, 54, 106]. Interesting recent results of Terrill et al. have shown that a chronic administration of the cysteine precursor 2-oxothiazolidine-4 carboxylate (OTC) markedly decreases the level of thiol oxidation in muscles of mdx mice; in parallel an amelioration of force and muscle morphology has been observed. Importantly the administration was not paralleled by an increase in cysteine or glutathione but rather by an increase in taurine level. The authors underlined that the decrease in taurine content may have a direct causative role in enhanced susceptibility to oxidative stress, disclosing a novel mechanism for beneficial effect of the classical anti-oxidant *N*-acetylcysteine [107].

Considering the mitochondrial sufferance occurring in dystrophic muscle [93], the previously described role of taurine for preserving mitochondrial function has to be taken into account for further studies. Similarly, the potential role of taurine and its chemical chaperone conjugate tauroursodeoxycholic acid in contrasting endoplasmic reticulum stress in various conditions should be considered for the acute and chronic ability of taurine to modulate signaling pathways [108, 109]. In addition, taurine may improve muscle metabolism by contrasting functional ischemia, based on the described vasodilating properties [110]. The clarification of the mechanism of action and the evaluation of long term safety and efficacy also at heart level can add important pre-clinical data to plan clinical trials in DMD patients (Table 1).

Taurine and disuse-related muscle atrophy

Muscle disuse is a general term which describes a condition of inactivity occurring after prolonged bed rest, spaceflight and/or aging. The slow-twitch muscles, devoted to postural maintenance, are the most affected ones, showing a slow-to-fast phenotype transition and severe atrophy, both leading to impaired muscle function. The adaptation of skeletal muscle to different activity includes changes in the expression of structural, metabolic and contractile proteins that fine-tune the characteristics of this tissue. The hindlimb unloaded (HU) model of disuse in rodents is a widely accepted ground-based model that mimics microgravity condition and is used to study the mechanisms responsible for the disuse-induced modification of skeletal muscle function. The soleus muscle of HU rats and mice becomes atrophic and experiences a slow-to-fast phenotype transition, characterized by an increased expression of the fast myosin heavy chain (MHC) isoform [111, 112]. Along the years, the studies on the HU model have shown that various proteins involved in the control of sarcolemma excitability, calcium ion homeostasis, energy metabolism, and contractile machinery undergo changes in the expression, turnover, and activity in accord with the entering of the slow muscle into a fast program [111, 113–117]. In particular, ClC-1 chloride and Nav1.4 sodium channels are differently expressed in fast-twitch and slow-twitch skeletal muscles, the expression of both being higher in the former. Accordingly with the change of phenotype, ClC-1 channel activity and expression as well as the intracellular resting calcium level in slow-twitch soleus muscle are significantly shifted by HU process toward the values of a fast muscle, even before the modification of MHC expression [111]. Similarly, HU increased sodium current density and sodium channel mRNA level in soleus muscle fibers [113]. All these changes alter the resistance to fatigue of antigravity muscle fibers, an effect that may contribute to the impairment of muscle function, in terms of excitability and contraction. A full understanding of the mechanisms of disuse-induced muscle alterations in humans is still incomplete and few molecules have been proposed for therapy [118, 119]. However, supplementation with essential amino acids and carbohydrates in combination with exercise attenuates muscle protein loss in humans exposed to prolonged inactivity [120, 121]. Based on these considerations and on our previous findings about the action of taurine in the modulation of calcium homeostasis and ion channel function [34, 41, 49], we focused on taurine as a potential candidate to counteract the HU-induced phenotype transition and skeletal muscle function impairment [1, 34].

In agreement with a critical role of taurine in phenotype-specific cellular function, the concentration of the amino acid is twofold higher in soleus compared to EDL muscle. The physiological relevance for this phenotypic difference is still unknown but various hypothesis can be raised based on the essential role of taurine in skeletal muscle and its actions in metabolism and phenotype-dependent properties. Interestingly, our recent findings [59] showed for the first time a marked reduction of taurine content in the soleus muscle of HU rat. This muscle loss would be consistent with an original report of National Aeronautics and Space Administration (NASA)

describing a large excretion of taurine in the urine of the astronauts of the APOLLO mission [122]. In spite of the reduction of taurine in soleus muscle of HU rats, the expression of TauT was unchanged. Indeed, TauT expression was found to be higher in slow-twitch soleus muscle with respect to the fast EDL, and was not reduced during HU, suggesting that the intracellular reduction of taurine is not associated with the change of phenotype. In addition, our data suggest that TauT activity is efficiently maintained during HU, since taurine oral supplementation fully prevents the loss of taurine content in HU-soleus muscle. Thus, we hypothesize that the reduction of intracellular taurine content during HU is likely due to increased taurine efflux. A possible explanation might be that taurine leakage compensates for intracellular osmolarity changes, which likely occurs due to muscle protein degradation and increased catabolism. Accordingly, the production of intracellular osmolytes during muscle disuse atrophy has been described, which may justify taurine escape in this condition [123–125]. Importantly in rats fed with taurine, TauT expression was reduced in soleus muscle, suggesting a negative feed-back regulation as a mechanism to control taurine intracellular level. As anticipated the TauT expression is under control of MEF2, a determinant of slow-fiber phenotype [79], thus it is tempting to speculate that TauT expression after taurine supplementation can be reduced by a mechanism involving a complex cross-talk between taurine and ClC-1 modulation during the phenotype transition.

Our findings also highlighted that taurine supplementation in HU rats has preserved resting gCl and resting cytosolic calcium level together with the slow MHC phenotype in the soleus muscle.

However, taurine had little effect on muscle atrophy, which is a severe condition occurring during HU as well as in various muscle diseases [126]. Indeed, it did not prevent the reduction of muscle-to-body weight ratio and of the fiber cross sectional area (CSA), while it partially contrasted the expression of atrogin-1 and mostly of muscle RING-finger protein-1 (MURF-1), two ubiquitin–proteasome pathway enzymes, that are strongly up-regulated as a result of HU-induced atrophy [127]. Such an effect suggests that a longer treatment or a different therapeutic schedule of taurine might have protective effect against muscle atrophy and might be useful to reach a complete muscular recovery. However complex mechanisms control the relative expression of atrogin and MURF-1 in skeletal muscle under various insults [79, 128] and further experiments are needed (Table 1).

Taurine and human skeletal muscle

Taurine has limited use in clinical settings although human use has been considered for specific diseases such as non-insulin dependent diabetes and related disorders, to treat alcohol withdrawal, congestive heart failure and arrhythmias, rheumatoid arthritis and other chronic inflammatory states, seizure disorders, and liver related disorders [19, 102, 129]. In Table 2 is a brief report of some clinical studies related to taurine supplementation, with relative dosages and outcomes. Most of them focused on diabetes mellitus, insulin resistance and diabetic complications, based on the rationale that plasma taurine concentration is reduced in patients with insulin-dependent diabetes mellitus (IDDM) [129–136]. Taurine was indicated in addition to specific drugs. Other clinical studies tested taurine in congestive heart failure, hypertension, inherited succinic semialdehyde dehydrogenase deficiency, obesity or its supplementation in aged individuals [137–143].

A part for the use in myotonic dystrophy patients [35–37], the potential therapeutic role of taurine for skeletal muscle disorders has yet to be verified in clinical settings. In fact, most of the studies about the role of taurine for skeletal muscle physiology and its potential in pathological conditions have been carried out in animal models. In these conditions taurine depletion or supplementation are directly correlated with changes in the amino acid content in skeletal muscle, which facilitate the drawing of conclusion about amino acid action and potential. However, few studies have been conducted in humans, and some contradictory reports are available, questioning about the actual usefulness of taurine supplementation or on its mechanism of action. Apart for the age-related changes reported in the previous paragraphs, one of the main issue concerns the modulation of taurine concentration in adult skeletal muscle under conditions of exercise and/or metabolic distress. Galloway et al. [144] demonstrated that taurine supplementation to exercised healthy adults leads to a marked increase in the amino acid plasma level that however is not paralleled, after 7 days of supplementation, by an increase in skeletal muscle. They proposed that intramuscular taurine concentration is tightly regulated and that high plasma level may actually work to reduce TauT activity in order to maintain constant the amino acid level. Therefore, even chronic oral taurine supplementation may cause less increase in human muscles than in rodent ones, and the observed muscle effects could be due to extracellular taurine actions. In addition, plasma levels are also tightly regulated via overexpression of TauT in kidney, which may also show specie-specific regulatory pathways [145, 146].

The dose is another important issue. In fact murine pre-clinical studies often require about tenfold higher concentration that in human trials; by the way this has to match the endogenous high level of taurine in target

Table 2 Clinical use of taurine in different pathophysiological conditions

References	Patients	Dose (g/day or mg/kg)	Duration	Result
Franconi et al. [130]	IDDM (Diabetes mellitus type 1)	1.5 g	90 days	No effect
Flizarova and Nedosugova [131]	IDDM	1 g	30 days	Glucose metabolism and trygliceride level improved
Chauncey et al. [133]	NIDDM (DM type 2)	3 g	4 months	Plasma taurine level increased
Brøns et al. [134]	Overweight non-diabetic	1.5 g	8 weeks	No effect
Xiao et al. [136]	Overweight non-diabetic	3 g	2 weeks	Insulin sensitivity improved
Nakamura et al. [132]	NIDDM with microalbuminemia	3 g	12 months	No effect
Moloney et al. [135]	IDDM	1.5 g	2 weeks	Endotelium-dependent reaction improved
Gonzales-Contreras et al. [142]	Cholestasis by parenteral nutrition	~25 mg/kg/day	~50 days	Hepatoprotection with reduction of AST, ALT and GGT
Rosa et al. [143]	Obesity	3 g/day	8 weeks	Increase in plasma levels of taurine and adiponectin; reduction of inflammatory markers
Pearl et al. [141]	Succinic semialdehyde dehydrogenase deficiency (efficacy, safety and tolerability)	50–200 mg/kg/d (age range 12 years)	13 months (mean time from 3 to 50)	No significant effects Tolerability issues at highest doses
Fujita et al. [139]	Hypertension	6 g	7 days	Systolic and diastolic pressure improved
Azuma et al. [138]	Congestive heart failure	6 g	4 weeks	Heart parameters improved
Bergamini et al. [137]	Epilepsy	200 mg–21 g	Various	Seizure frequency reduction
Durelli et al. [36]	Dystrophic myotonia	6–10 g	6 months	Myotonic symptoms improvement
Dunn-Lewis et al. [140]	Elderly	500 mg in multinurtient supplement	4 weeks	Physical function improved

organs. In addition, an accurate muscle exposure to taurine after oral ingestion requires a careful assessment of the pharmacokinetic profile that has not been extensively evaluated in humans. In line with Galloway et al. [144], a single oral dose of 4 g in healthy volunteers allows to get a maximal plasma peak in about 1.5 h and showed an half-life of 1 h with a first-order kinetic clearance; this is in line with kidney being the main organ regulating taurine level [147]. Generally the daily dose of taurine ranges between 3 and 6 g; consequently its fast kinetic can account for some of the puzzling data obtained, suggesting the need of a more careful determination of the optimum dose. It is important to underline that most of the available evidences focus on the usefulness of taurine supplementation in sustaining muscle function in trained individuals. Balshaw et al. have recently evaluated the outcome of 1 g taurine ingestion, evaluated in blind against placebo, on running performance of trained middle-distance runners. They described a modest, although significant, increase in performance in the taurine-treated group, without any change in metabolism parameters [148]. The authors claimed that a similar improvement of performance after taurine ingestion, without changes in oxygen uptake or plasma lactate, has been found in other studies [144]. Taurine muscle levels were not assessed, thus the correlation between taurine effect and a specific muscle action is rather indirect. Accordingly, they speculated about alternative potential mechanisms, such as the action of taurine at muscle membrane level, in preventing taurine drop during exercise or rather an effect on neuronal function.

In another study, a combination of taurine (2 g) and branched-chain amino acids three times a days for 2 weeks before eccentric exercise, plus 4 days after, has been tested in healthy untreated volunteers. The eccentric exercise protocol consisted of repeated sets elbow flexion at 90° to an extended position, finally leading to uncontrolled damaging stretch. The combination exerted a greater protection against muscle damage and delayed-onset muscle soreness than single administrations, although no detailed investigation has been done to clarify the mechanism of action and/or the amino acid level into the muscle [149]. Similarly, da Silva et al. have recently described the ability of 14 days taurine

administration to increase strength of the elbow flexor subjected to eccentric exercises in young adult males; in parallel, markers of oxidative stress were reduced, without increase in endogenous anti-oxidant expression nor changes in inflammatory markers. Again muscle taurine level were not determined [150]. Therefore the available evidences do not allow to conclude about the ability of supplemented taurine to actually increase its muscle level in adult healthy and trained individuals, suggesting alternative modality of action, i.e. at neuromuscular system. However, it cannot be ruled out that taurine supplementation may effectively enhances muscle taurine levels in conditions characterized by more dramatic fluctuation of its content. This applies to postnatal development and aging, and mostly to pathological conditions such as muscular dystrophy and disuse-related muscle dysfunction (Table 1) [151]. More direct evidences in humans and patients will be helpful, in order to better correlate the effect of exogenous administration of taurine with the ability of residual muscle tissue to uptake the right amount, or rather to disclosure taurine actions independent on its intracellular levels [145]. In addition, an inter-individual variation in plasma increase of taurine after supplementation may occur in relation to both nutritional state, age, drug interaction, while gene polymorphism in taurine transporter or modulation of its function and/or expression by cell metabolic state or activation of transcription factors may affect the actual level of taurine being transported into the myofibers [134, 146, 152–154]. Hence caution should be taken when concluding about lack of taurine usefulness for human muscular system without an adequate control of all variables.

Conclusion

We herein summarized the results obtained in about 30 years of research on taurine and skeletal muscle by us and other research groups. Taurine is far from themes of fashion science or from immediate interest in innovative drug development by Pharma Companies. Nevertheless the reason for such a long interest is that taurine acquired over the years a special appeal for its puzzling and multiple effects. We underlined the ability of taurine to control the function of ion channels and consequently membrane excitability as well as calcium homeostasis and excitation–contraction coupling. It has been highlighted that novel evidences are emerging regarding taurine mechanism of action, ranging from modulation of muscle metabolism to control of gene transcription, as well as in the specie-specific mechanisms underlying its intracellular levels in both chronic and acute conditions. These make the research on the topic "taurine and skeletal muscle" a continuous source of novel and exciting results allowing to renew the enthusiasm and novel working hypotheses. The wide and interconnected effects observed support a key role of the amino acid to ensure a proper muscle function and reinforce its interest as therapeutic agent in various inherited and acquired muscular disorders. The available evidences favor a greater effect of taurine in diseased condition accompanied by alterations in taurine concentration in muscle; similar benefit can occur in conditions where fluctuation in taurine level take place such as exercise, protein content in diet or post-natal development. Both acute and chronic effects of taurine supplementation are feasible, and likely occur with different time-scale although similarly interesting and important. Although a careful distinction has not been made, it is predictable that acute effects of taurine are better appreciable in situations of rapid fluctuations such as exercise, or when involving direct modulation of ion channel, or on muscles that are more dependable of external taurine such as fast-twitch ones. In parallel, chronic taurine effects, likely accompanied by changes in intracellular content, could be of value for long term control of neuromuscular function in progressive conditions, such as muscular dystrophy and disuse or aging-related dysfunction. At this regard more evidences are necessary to better understand the interest of taurine for ensuring a proper muscle function in human other than in animals. Consequently, a more clinically-oriented research will help to support the interest of taurine as novel and safer therapeutic approach of rare inherited muscle diseases and other myopathic states.

Authors' contributions

ADL: have made a substantial contribution in designing and writing the review, updating current literature and in interpretation of available data in the field; SP: was significantly involved in writing, in figures and table organizations, literature search and interpretation of available information; DCC: critically revised the manuscript and its organization and gave a substantial support to the finalization of the work. All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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B6

Patient Information

Patient: B6
Patient Number: B6
Breed: lab mix
Exam Date: 01/10/2018 08:21

Age: 6 years
Weight:(kg) 25.10
Sex: F
BSA: 0.87

Referring Veterinarian: B6
Cardiologist: B6
Client Number: 147921

History: B6 was presented for evaluation of cough, labored breathing, multiple episodes of collapse, cardiomegaly, and suspected congestive heart failure. B6 was initially seen by her rDVM on December 30th for cough. She was initially treated with a humidifier, B6, and a decrease in length of walks and did not improve. On January 4th she had a collapse episode during which she circled, fell over, and flopped for about a minute. She has a second less severe episode on January 5th. Labwork at this date showed mild elevation of ALT and AST with mild increase in CK. T4 was low normal. She has continued to be short of breath and tires easily. She chased a squirrel a couple of days ago and stood with a wide based stance afterward. She is on year-round heartworm, flea and tick preventative and was last tested negative for heartworm 9/9/17. She eats California Natural Kangaroo and Red Lentil dry food with vegetables and 2 tbsp of canned pumpkin. She is on B6 B6 twice daily and B6 The B6 was discontinued yesterday.

Physical Examination: T 102.7 P 208 R 150. Grade 3/6 left apical systolic murmur and gallop. Regular tachycardia. Quiet heart sounds. Localized fine crackles left cranial hilar region, dry cough. Poor femoral pulses. Unremarkable abdominal palpation. mm pale pink, normal refill. Hydration OK. Normal PLNs.

Diagnostic Tests: 1/10/18:

B6

Echo - see below. Sinus tachycardia on ECG.
Taurine level (whole blood): pending, will call with results.

B6

B6

Thoracic radiographs: Mild decrease in severity of cardiomegaly (as compared to rDVM films from 1/9/18). Resolving cardiogenic edema.

Hospitalization:
An IV catheter was placed and B6 was hospitalized in ICU with continuous ECG monitoring. She was started on B6 and B6 in AM and 10 mg in PM). She did well overnight with an improvement in respiratory rate/effort. B6 had occasional short paroxysms of "slow" ventricular tachycardia (160-270 bpm) that were noted noted to persist beyond ~7 pm.

B6 was started on B6 the following morning. She continued to do well with a normal appetite and improved respiratory rate.

Echocardiographic Report

2D ECHO
LA Systolic Diameter LX

DOPPLER
AV Peak Velocity
AV Peak Gradient
MR Peak Velocity
PV Peak Velocity

M-MODE
LV Diastolic Diameter MM
LV Systolic Diameter MM
LV Fractional Shortening MM
LV Diastolic Volume Cube
LV Systolic Volume Cube
LV Ejection Fraction Cube
IVS Diastolic Thickness MM
IVS Systolic Thickness MM
IVS Percent Thickening MM

B6

PV Peak Gradient
TR Peak Velocity
TR Peak Gradient

LVPW Diastolic Thickness MM
LVPW Systolic Thickness MM
LVPW Percent Thickening MM
IVS to PW Ratio MM
LV Mass MM
LV Mass Normalized MM
RV Diastolic Diameter MM
LA Systolic Diameter MM
Aortic Root Diameter MM

B6

Left Ventricle:	Severe dilation (normalized LVIDd 2.85) with severe myocardial dysfunction (normalized LVIDs 2.34). Increased sphericity.
Left Atrium:	Severe dilation.
Right Ventricle:	Mild dilation with subjective decrease in contractility.
Right Atrium:	Mild dilation.
Mitral Valve:	Normal valve morphology. 4+ central mitral regurgitation.
Aortic Valve:	Normal.
Tricuspid Valve:	Mildly thickened valve leaflets. 1+ tricuspid regurgitation. Normal regurgitant velocities.
Pulmonic Valve:	Mildly thickened valve leaflets. Mild pulmonic insufficiency.
Aorta:	Normal
Pericardium:	Normal

Diagnosis

Dilated cardiomyopathy - This is a disease characterized by weakening of the heart muscle and dilation of the heart chambers. As the disease progresses, it can lead to congestive heart failure (fluid in the lungs causing shortness of breath and cough). Abnormal heart rhythms are common and can result in sudden death. Most commonly this is an inherited disease, though it can occur secondary to a deficiency in an amino acid called taurine.

Left sided congestive heart failure

Recommendations

Give all medications as directed:

B6

One thing that can be very helpful for home monitoring is checking sleeping or resting respiratory rates. A recent study showed that even pets with severe heart disease rarely have resting respiratory rates greater than 30 breaths per minute unless they are starting to decompensate for that disease. Elevated respiratory rates at home may be even more sensitive than chest radiographs at picking up early decompensation. Count your pet's respiratory rate when he/she is at rest or sleeping (not within 20 minutes of being active). If his/her respiratory rate is greater than 30 breaths per minute, recheck again in a couple of hours. If persistently elevated above this level, call.

With advanced heart disease, our biggest dietary concerns are adequate calorie content and low sodium content. We aim for less than 80mg sodium per 100 kilocalories (kcal) in patients that have developed congestive heart failure. We do not advise protein restriction unless there is concurrent kidney disease (i.e. kidney diets are not advised unless there is concurrent kidney disease). Please refer to our diet handouts with a list of currently adequate diets and treats, though this list is not exclusive. If you wish to feed a diet that is not on these lists, you will need to call the manufacturer of the diet to obtain a sodium content.

As we discussed, we have had three other cases of severe DCM where the dogs have been eating a kangaroo and lentil diet. There is no data that has shown an association with this diet and DCM but we are concerned there may be a connection there and are looking into it at this time. For this reason, we would consider changing B6 diet.

We sent B6 home with a few cans of Hill's Science Diet Canine Maintenance canned food. This food has an appropriate level of sodium for dogs in congestive heart failure and is available at most pet stores. Lamb should be avoided as a protein source but any other protein is appropriate (with the exception of kangaroo).

The very best diet for dogs with DCM/heart failure is probably Hill's Science Diet Prescription j/d. This food has a good source of taurine, carnitine and fatty acids. However, this diet is rather costly.

We have submitted a taurine level and will call you with the results when they are available.

Exercise is also a concern in advanced heart disease. While cage rest is ideal with active heart failure, some exercise is permissible in asymptomatic disease. However, vigorous or extended exercise should be avoided.

***As long as B6 does well at home we would like to re-evaluate her in 7-10 days. At this time we will recheck her kidney values/electrolytes and blood pressure as well as repeat chest x-rays.

B6 DVM, DACVIM (Cardiology)

(Electronically Signed)

Final Date:

Like us on Facebook!

www.facebook.com B6

Notes to our clients

-Please bring all medications to your pet's scheduled appointments.

-We require a 48 hour notice for all refills. When you call to request a refill, please leave the pharmacy phone number or clearly indicate if you plan on picking up the medication at our facility. PRESCRIPTION REFILLS ARE NOT AVAILABLE AFTER B6 REGULAR BUSINESS HOURS (Evenings, Fridays, holidays and weekends).

-Check out B6 and enter your local zip code to search for the best prices on your medications at your local pharmacies.

-If an emergency arises with your pet, B6 is a 24 hour facility.

B6

Sample Submission Form

UC CUSTOMERS ONLY:
Non-federal funds ID/Account Number to bill:_____

Amino Acid Laboratory
University of California, Davis
1020 Vet Med 3B
1089 Veterinary Medicine Drive
Davis, CA 95616
Tel: (530)752-5058, Fax: (530)752-4698

http://www.vetmed.ucdavis.edu/vmb/aal/aal.html

Vet/Tech Contact: Account # B6 / Contact: B6 Date: 1-10-18
Company Name: B6
Address: B6

Email: B6
Tel: B6 **Fax:** B6

Billing Contact: B6 **TAX ID:**_____
Email: B6 **Tel:** B6

Patient Name: B6
Species: K9
Owner's Name: B6

Sample Type: ☐ Plasma ☑ Whole Blood ☐ Urine ☐ Food ☐ Other:_____
Test Items: ☑ Taurine ☐ Complete Amino Acid ☐ Other:_____

Taurine Results (nmol/ml)

Plasma:_ _ Whole Blood B6 Urine:_____ Food:_____

Reference Ranges (nmol/ml)

	Plasma		Whole Blood	
	Normal Range	No Known Risk for Taurine Deficiency	Normal Range	No Known Risk for Taurine Deficiency
Cat	80-120	>40	300-600	>200
Dog	60-120	>40	200-350	>150

B6

Patient Information

Patient: B6
Patient Number: B6

Age: 8 years
Weight:(kg) 29.40

Referring Veterinarian: B6
Cardiologist: B6 DVM, DACVIM (Cardiology)

Breed: Labrador Retriever
Exam Date: B6 08:22

Sex: F
BSA: 0.96

Client Number: 138074

History: B6 was presented to the Emergency Service last night for transfer to Cardiology for further evaluation of her heart. She was seen by B6 s last week after collapsing last Thursday while playing fetch with her owner. On presentation at B6 she was found to be in atrial fibrillation with evidence of mild heart failure. She was treated with a B6 overnight, then B6 as well as B6. Her heart rhythm converted back to sinus rhythm as of B6 (Friday). She was presented back to B6 on Saturday after collapsing again on Saturday while playing fetch. She was found to still be in a normal heart rhythm and radiographs showed resolution of heart failure at that time. Bloodowrk done at B6 (CBC and chem) was reported as unremarkable.

Physical Examination: Grade 3-4/6 left apical holosystolic murmur. Irregular rhythm consistent with sinus arrhythmia. Clear lungs. Moderate femoral pulses. Normal abdominal palpation. Well hydrated. Normal PLNs. mm pink, CRT normal

Diagnostic Tests: B6

Telemetry - B6 heart rhythm was monitored throughout her hospital stay and showed a consistent sinus rhythm/arrhythmia with no significant dysrhythmias.

B6

Echocardiographic Report

2D ECHO
LA Systolic Diameter LX

DOPPLER
AV Peak Velocity
AV Peak Gradient
Mitral E Point Velocity
Mitral E to A Ratio
MR Peak Velocity

M-MODE
LV Diastolic Diameter MM
LV Systolic Diameter MM
LV Fractional Shortening MM
LV Diastolic Volume Cube
LV Systolic Volume Cube
LV Ejection Fraction Cube
IVS Diastolic Thickness MM
IVS Systolic Thickness MM
IVS Percent Thickening MM

B6

Aortic Root Diameter

PV Peak Velocity
PV Peak Gradient
TR Peak Velocity
TR Peak Gradient

LVPW Diastolic Thickness MM
LVPW Systolic Thickness MM
LVPW Percent Thickening MM
IVS to PW Ratio MM
LV Mass MM
LV Mass Normalized MM
LA Systolic Diameter MM
Aortic Root Diameter MM
MV E Point Septal Separation

B6

Left Ventricle: Dilated, rounded, and poorly contractile chamber.

Left Atrium: Moderate dilation with marked dilation of right pulmonary vein.

Right Ventricle: Normal.

Right Atrium: Normal.

Mitral Valve: Mildly thickened valve leaflets. 4+ eccentric regurgitation. High inflow velocity with restrictive filling pattern.

Aortic Valve: Normal.

Tricuspid Valve: Thickened valve leaflets with multiple 1+ jets of regurgitation. TR velocity is increased consistent with mild pulmonary hypertension.

Pulmonic Valve: Mild valve thickening. 1+ regurgitation. PI velocity is not suggestive of diastolic pulmonary hypertension.

Aorta: Normal.

Pericardium: Normal.

Diagnosis

Dilated cardiomyopathy - This is a disease characterized by weakening of the heart muscle and dilation of the heart chambers. It is most commonly an inherited disease, but can occur as a consequence of other injuries to the heart. Severe valvular heart disease can sometimes lead to heart muscle failure (cardiomyopathy of overload) and since B6 appears to have severe valve disease as well as heart muscle failure, we cannot be sure whether one led to the other or if there are two completely separate disease processes. As the disease progresses, it can lead to congestive heart failure (fluid in the lungs causing shortness of breath and cough). Abnormal heart rhythms are common and can result in sudden death. Most commonly this is an inherited disease, though it can occur secondary to a deficiency in an amino acid called taurine.

Chronic degenerative valve disease - Degenerative changes in one or more heart valves have caused leaking across these valves. This is the source of the heart murmur. As this disease progresses, the heart enlarges. Eventually this can lead to symptoms of cough and shortness of breath (airway compression and/or congestive heart failure).

Atrial fibrillation on presentation at B6 converted back to sinus rhythm 1/21/17 - This is a chaotic and rapid heart rhythm from the upper heart chambers. It most commonly occurs secondary to severe underlying heart diseases, though it can occur in isolation in some giant breed dogs. Our goal medically in treating this arrhythmia is to control the heart rate, but B6 has returned to a normal heart rhythm so no specific medication is indicated for the heart rhythm at this time.

Exertional collapse - I suspect the first episode was likely caused by the new onset of the atrial fibrillation in B6 but the second episode is a little harder to explain. We did not find any evidence while monitoring her in the hospital of other arrhythmia, and she had a normal heart rhythm at the emergency visit after her second collapse as well. It is possible that she collapsed as a result of her severe structural heart disease, though this is a little surprising to see recurrent collapse after starting on medications that had been effective in resolving her heart failure.

Recommendations

Please DISCONTINUE:

B6

With advanced heart disease, our biggest dietary concerns are adequate calorie content and low sodium content. We aim for less than 80mg sodium per 100 kilocalories (kcal) in patients that have developed congestive heart failure. We do not advise protein restriction unless there is concurrent kidney disease (i.e. kidney diets are not advised unless there is concurrent kidney disease). Please refer to our diet handouts with a list of currently adequate diets and treats, though this list is not exclusive. If you wish to feed a diet that is not on these lists, you will need to call the manufacturer of the diet to obtain a sodium content.

One thing that can be very helpful for home monitoring is checking sleeping or resting respiratory rates. A recent study showed that even dogs with severe heart disease rarely have resting respiratory rates greater than 30 breaths per minute unless they are starting to decompensate for that disease. Elevated respiratory rates at home may be even more sensitive than chest radiographs at picking up early decompensation. Count your pet's respiratory rate when he/she is at rest or sleeping (not within 20 minutes of being active). If his/her respiratory rate is greater than 30 breaths per minute, recheck again in a couple of hours. If persistently elevated above this level, call.

Exercise is also a concern in advanced heart disease. While cage rest is ideal with active heart failure, some exercise is permissible in asymptomatic disease. However, vigorous or extended exercise should be avoided.

Please call if you have any concerns about B6 if she develops an increase in respiratory rate or effort, has a persistent cough, or has any further collapse episodes. As long as she is doing well, we will plan to recheck her again in another month and will recheck her heart rhythm, chest radiographs, and kidney panel at that time.

B6 DVM, DACVIM (Cardiology)

(Electronically Signed)

Final Date: B6 6:50
Amended: 17:16

Like us on Facebook!
www.facebook.com B6

Notes to our clients
-Please bring all medications to your pet's scheduled appointments.
-We require a 48 hour notice for all refills. When you call to request a refill, please leave the pharmacy phone number or clearly indicate if you plan on picking up the medication at our facility. PRESCRIPTION REFILLS ARE NOT AVAILABLE AFTER B6 REGULAR BUSINESS HOURS (Evenings, Fridays, holidays and weekends).
-Check o B6 and enter your local zip code to search for the best prices on your medications at your local pharmacies.
-If an emergency arises with your pet B6 spital is a 24 hour facility.

B6

Patient Information

Patient: B6
Patient Number: B6
Age: 9 years
Weight:(kg) 29.30
Referring Veterinarian: B6
Cardiologist: B6 DVM, DACVIM (Cardiology)
Breed: Labrador Retriever
Sex: FS
Client Number: 138074
Exam Date: 05/31/2017 14:13
BSA: 0.96

History: B6 was presented for reevaluation of dilated cardiomyopathy, chronic degenerative valve disease, historical atrial fibrillation with collapse and historical CHF. B6 continues to do well at home without any episodes of collapse or weakness. B6 has good energy levels, with a normal appetite and eliminations. She is breathing comfortably without an increase in rate or effort and her resting respiratory rates have been averaging 25bpm. Within the last 2-3 days, B6 has been very anxious and not as social due to severe storm anxiety. B6 is also on a daily B6 supplement.

Physical Examination: B6 Grade 3-4/6 left apical holosystolic murmur.

B6

Diagnostic Tests:

Thoracic radiographs: Mild progression of cardiac enlargement with no evidence of cardiac decompensation.

B6

Echocardiogram: See below. ECG during echo showed a normal sinus rhythm.

Echocardiographic Report

2D ECHO
LA Systolic Diameter LX

DOPPLER
AV Peak Velocity
AV Peak Gradient
MR Peak Velocity
PV Peak Velocity
PV Peak Gradient
TR Peak Velocity
TR Peak Gradient

M-MODE
LV Diastolic Diameter MM
LV Systolic Diameter MM
LV Fractional Shortening MM
LV Diastolic Volume Cube
LV Systolic Volume Cube
LV Ejection Fraction Cube
IVS Diastolic Thickness MM
IVS Systolic Thickness MM
IVS Percent Thickening MM
LVPW Diastolic Thickness MM
LVPW Systolic Thickness MM
LVPW Percent Thickening MM
IVS to PW Ratio MM
LV Mass MM
LV Mass Normalized MM
LA Systolic Diameter MM
Aortic Root Diameter MM
MV E Point Septal Separation

B6

B6

Left Ventricle: Minimal decrease in diastolic dimension with mild decrease in systolic dimension. Persistent moderate decrease in global contractility.

Left Atrium: Moderate dilation, minimal decrease since initial study.

Right Ventricle: Normal.

Right Atrium: Normal.

Mitral Valve: Mildly thickened valve leaflets. 3-4+ regurgitation.

Aortic Valve: Normal.

Tricuspid Valve: 1+ regurgitation. TR velocity consistent with normal pulmonary pressures.

Pulmonic Valve: 1+ regurgitation. Normal PI velocity.

Aorta: Normal.

Pericardium: Normal.

Diagnosis

Dilated Cardiomyopathy
Chronic Degenerative Valve Disease
Historical atrial fibrillation with collapse B6 continues to be in a normal sinus rhythm today
Historical congestive heart failure - no evidence of heart failure today

B6 echo today looks stable to slightly improved from his initial echo in January, though his heart is a little larger today than on the radiographs in February. He is showing no signs of recurrent heart failure and his heart rhythm is still normal. Overall, I am happy with where we are overall.

Recommendations

B6

As long as B6 continues to do well, we will continue to recheck her every 3-4 months with chest radiographs, renal panel, and blood pressure with periodic echocardiograms. Please call, however, if she develops any new or recurrent clinical symptoms.

B6 DVM, DACVIM (Cardiology)

(Electronically Signed)
Final Date: 31 May 2017 15:11

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www.facebook.com B6

Notes to our clients
-Please bring all medications to your pet's scheduled appointments.
-We require a 48 hour notice for all refills. When you call to request a refill, please leave the pharmacy phone number or clearly indicate if you plan on picking up the medication at our facility. PRESCRIPTION REFILLS ARE NOT AVAILABLE AFTER B6 S REGULAR BUSINESS HOURS (Evenings, Fridays, holidays and weekends).
-Check out B6 and enter your local zip code to search for the best prices on your medications at your local pharmacies.
-If an emergency arises with your pet, B6 pital is a 24 hour facility.

B6

Patient Information

Patient: B6

Patient Number: B6

Age: 9 years

Weight:(kg) 32.10

Referring Veterinarian: B6

Cardiologist: B6 DVM, DACVIM (Cardiology)

Breed: Lab

Sex: F

Client Number: 138074

Exam Date: 12/11/2017 08:17

BSA: 1.02

History: Reevaluation of dilated cardiomyopathy with chronic degenerative valve disease, historical atrial fibrillation with collapse, historical congestive heart failure, and urinary incontinence. B6 is doing well at home. Owners do report a new cough with him since his last visit. It is not frequent and is seen at rest and with excitement/activity. She is breathing comfortably. She has a normal appetite and good activity level as well. Owners are transitioning her to a new brand of venison food.

Physical Examination: B6 Grade 3/6 left apical systolic murmur with wide radiation. B6 B6

Diagnostic Tests: Chest radiographs: progressive cardiomegaly with VHS 13.5 versus 13 on radiographs in September, normal pulmonary vessels, unchanged lung pattern with no evidence of active heart failure

B6

Echocardiographic Report

2D ECHO
LA Systolic Diameter LX

DOPPLER
AV Peak Velocity
AV Peak Gradient
Mitral E Point Velocity
Mitral E to A Ratio
MR Peak Velocity

M-MODE
LV Diastolic Diameter MM
LV Systolic Diameter MM
LV Fractional Shortening MM
LV Diastolic Volume Cube
LV Systolic Volume Cube
LV Ejection Fraction Cube
IVS Diastolic Thickness MM
IVS Systolic Thickness MM
IVS Percent Thickening MM
LVPW Diastolic Thickness MM

B6

Aortic Root Diameter

PV Peak Velocity
PV Peak Gradient
TR Peak Velocity
TR Peak Gradient

LVPW Systolic Thickness MM
LVPW Percent Thickening MM
IVS to PW Ratio MM
LV Mass MM
LV Mass Normalized MM
RV Diastolic Diameter MM
LA Systolic Diameter MM
Aortic Root Diameter MM
MV E Point Septal Separation

B6

Left Ventricle: Stable diastolic dimension with progressive increase in systolic dimension and decline in myocardial function.

Left Atrium: Progressive dilation.

Right Ventricle: Mild dilation.

Right Atrium: Mild dilation.

Mitral Valve: Unchanged mild thickening with 3-4+ regurgitation.

Aortic Valve: Normal. Acceleration slope is decreased.

Tricuspid Valve: Two jets of 2+ regurgitation. TR velocity consistent with normal pulmonary pressures.

Pulmonic Valve: Normal. 1+ physiologic regurgitation.

Aorta: Normal.

Pericardium: Normal.

Diagnosis

Dilated cardiomyopathy with chronic degenerative valve disease - B6 heart is bigger and does not contract as well as it did at her last two rechecks. However, she is showing no signs of decompensation at this time.
Historical atrial fibrillation with collapse
Historical congestive heart failure
B6

Recommendations

B6

Please call if you have any questions or concerns about B6. As long as she continues to do well, we will recheck her again in another 3-4 months. We will do a brief echo and recheck kidney values and blood pressure at that visit +/- chest radiographs (if she is having any respiratory symptoms).

B6 DVM, DACVIM (Cardiology)

(Electronically Signed)
Final Date: 11 December 2017 14:48
Amended: 11 December 2017 14:49

Like us on Facebook!

www.facebook.com B6

Notes to our clients

-Please bring all medications to your pet's scheduled appointments.

-We require a 48 hour notice for all refills. When you call to request a refill, please leave the pharmacy phone number or clearly indicate if you plan on picking up the medication at our facility. PRESCRIPTION REFILLS ARE NOT AVAILABLE AFTER B6 REGULAR BUSINESS HOURS (Evenings, Fridays, holidays and weekends).

-Check out B6 and enter your local zip code to search for the best prices on your medications at your local pharmacies.

-If an emergency arises with your pet B6 ital is a 24 hour facility.

B6

Sample Submission Form

Amino Acid Laboratory
University of California, Davis
1020 Vet Med 3B
1089 Veterinary Medicine Drive
Davis, CA 95616
Tel: (530)752-5058, Fax: (530)752-4698

http://www.vetmed.ucdavis.edu/vmb/aal/aal.html

UC CUSTOMERS ONLY:
Non-federal funds ID/Account Number to bill:_____

Vet/Tech Contact: Account # B6 / Contact B6 **Date:** 1-23-17
Company Name: B6
Address: B6
B6
Email: B6
Tel: B6 **Fax:** B6

Billing Contact: B6 **TAX ID:**
Email: B6 **Tel:** B6

Patient Name: B6
Species: hg
Owner's Name: B6

Sample Type: ☐ Plasma ☑ Whole Blood ☐ Urine ☐ Food ☐ Other:_____
Test Items: ☑ Taurine ☐ Complete Amino Acid ☐ Other:_____

Taurine Results (nmol/ml)

Plasma:_____ Whole Blood: B6 Urine:_____ Food:_____

Reference Ranges (nmol/ml)

	Plasma		Whole Blood	
	Normal Range	No Known Risk for Taurine Deficiency	Normal Range	No Known Risk for Taurine Deficiency
Cat	80-120	>40	300-600	>200
Dog	60-120	>40	200-350	>150

B6

Patient Information

Patient: B6

Patient Number: B6

Age: 5 years

Weight:(kg) 25.60

Referring Veterinarian: B6

Cardiologist: B6 DVM, DACVIM (Cardiology)

Breed: Labrador Retriever

Sex: FS

Client Number: 138074

Exam Date: 08/24/2017 08:19

BSA: 0.88

History: B6 was presented to B6 today for evaluation of a new heart murmur and evaluation after being diagnosed with congestive heart failure on B6 B6 was evaluated by her regular vet on B6 for heavy breathing and coughing. Radiographs and blood work were done at the time and B6 was diagnosed with an enlarged heart and congestive heart failure at that time. B6 was started on B6 by her regular vet. B6 was seen through B6 ER on B6 for reevaluation of congestive heart failure. The clients report that B6 had improved some but had not improved a lot. Medications were adjusted based on recommendations from B6 e on B6 until B6 could get an appointment to be see by B6. The clients report that since the medications were increased B6 has improved, however they do still feel that she is breathing faster than normal at home and she is still panting a lot at home. B6 is still eating very well at home and is currently on a low sodium kangaroo and lentil diet. The clients also report that there other dog, B6, who we also see is B6 aunt (B6 mother was a littermate of B6). B6 t which started prior to developing congestive heart failure and initiation of treatment. The clients report that B6 was not well controlled on B6 tablets: 1 tablet by mouth once daily so B6 tablets: Give 1/2 tablet by mouth every 12 hours was added in. They are unsure if B6 is now controlled because there other dog has developed B6 as well. The client feel that B6 is less social and less active at home. B6 is currently receiving B6 give 1 and 1/2 tablets by mouth every 12 hours, B6 : give 1 tablet by mouth every 12 hours, B6 : give 1 tablet by mouth every 12 hours, B6 : give 1 and 1/2 tablets by mouth every 12 hours, B6 : give 1 tablet by mouth once every 24 hours, B6 : give 1/2 tablet by mouth every 12 hours and B6 give 3/4 tablet by mouth every 24 hours.

Physical Examination: B6

Grade 4/6 left apical systolic murmur with radiation to the right. Adequate femoral pulses. Regular

Diagnostic Tests: B6

Thoracic Radiographs: Persistent cardiomegaly with mild decrease in severity. No evidence of cardiac decompensation.

B6

Echocardiographic Report

2D ECHO
LA Systolic Diameter LX

DOPPLER
AV Peak Velocity
AV Peak Gradient
Mitral E Point Velocity
Mitral E to A Ratio
MR Peak Velocity

M-MODE
LV Diastolic Diameter MM
LV Systolic Diameter MM
LV Fractional Shortening MM
LV Diastolic Volume Cube
LV Systolic Volume Cube
LV Ejection Fraction Cube
IVS Diastolic Thickness MM
IVS Systolic Thickness MM

B6

Aortic Root Diameter

PV Peak Velocity
PV Peak Gradient
TR Peak Velocity
TR Peak Gradient

IVS Percent Thickening MM
LVPW Diastolic Thickness MM
LVPW Systolic Thickness MM
LVPW Percent Thickening MM
IVS to PW Ratio MM
LV Mass MM
LV Mass Normalized MM
MV E Point Septal Separation

B6

Left Ventricle: Severe dilation with marked global myocardial dysfunction. Normalized LVIDd 2.9, normalized LVIDs 2.38.

Left Atrium: Severe dilation with septum bowing to the right.

Right Ventricle: Mild to moderate dilation with reduced myocardial function.

Right Atrium: Mild to moderate dilation.

Mitral Valve: Thickened valve leaflets. 3-4+ mitral regurgitation.

Aortic Valve: Mildly thickened valve leaflets. No aortic insufficiency.

Tricuspid Valve: Thickened valve leaflets. Two jets of 2-3+ tricuspid regurgitation. Normal regurgitant velocities.

Pulmonic Valve: Mildly thickened valve leaflets. Mild pulmonic insufficiency.

Aorta: Normal

Pericardium: Normal

Diagnosis

Endocardiosis (chronic degenerative valve disease) - Degenerative changes in one or more heart valves have caused leaking across these valves. This is the source of the heart murmur. As this disease progresses, the heart enlarges. Eventually this can lead to symptoms of cough and shortness of breath (airway compression and/or congestive heart failure). This is usually a slowly progressive disease.

Dilated cardiomyopathy - This is a disease characterized by weakening of the heart muscle and dilation of the heart chambers. As the disease progresses, it can lead to congestive heart failure (fluid in the lungs causing shortness of breath and cough). Abnormal heart rhythms are common and can result in sudden death. Most commonly this is an inherited disease, though it can occur secondary to a deficiency in an amino acid called taurine.

Recommendations

Please continue the following medications as previously directed:

B6

As we discussed, B6 unfortunately have very similar structural heart disease. Since they are related, this raises concern for a genetic component. You have expressed that there is no history of heart disease in their lineage. It is possible that the disease has remained silent in other related dogs or is inherited in a way that it is only expressed in certain individuals. The other common denominator that B6 have is the kangaroo diet. Even though we have not specifically associated this protein source with taurine/carnitine deficiency, it may be warranted to consider a diet with a different protein source since it is a novel protein and both dogs have very similar disease manifestations. Lamb should be avoided as it has been associated with taurine deficiency in dogs.

We did not check B6 blood taurine level today- since B6 was normal it is highly unlikely that B6 will be deficient as they are related and eat the same food.

One thing that can be very helpful for home monitoring is checking sleeping or resting respiratory rates. A recent study showed that even pets with severe heart disease rarely have resting respiratory rates greater than 30 breaths per minute unless they are starting to decompensate for that disease. Elevated respiratory rates at home may be even more sensitive than chest radiographs at picking up early decompensation. Count your pet's respiratory rate when he/she is at rest or sleeping (not within 20 minutes of being active). If his/her respiratory rate is greater than 30 breaths per minute, recheck again in a couple of hours. If persistently elevated above this level, call.

With advanced heart disease, our biggest dietary concerns are adequate calorie content and low sodium content. We aim for less than 80mg sodium per 100 kilocalories (kcal) in patients that have developed congestive heart failure. We do not advise protein restriction unless there is concurrent kidney disease (i.e. kidney diets are not advised unless there is concurrent kidney disease). Please refer to our diet handouts with a list of currently adequate diets and treats, though this list is not exclusive. If you wish to feed a diet that is not on these lists, you will need to call the manufacturer of the diet to obtain a sodium content.

Exercise is also a concern in advanced heart disease. While cage rest is ideal with active heart failure, some exercise is permissible in asymptomatic disease. However, vigorous or extended exercise should be avoided.

***As long as B6 does well at home we would like to re-evaluate her in 4-6 weeks. At this time we will recheck her kidney values/electrolytes and blood pressure as well as repeat chest x-rays.

B6, DVM, DACVIM (Cardiology)

(Electronically Signed)

Final Date:

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Notes to our clients

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-We require a 48 hour notice for all refills. When you call to request a refill, please leave the pharmacy phone number or clearly indicate if you plan on picking up the medication at our facility. PRESCRIPTION REFILLS ARE NOT AVAILABLE AFTER B6 'S REGULAR BUSINESS HOURS (Evenings, Fridays, holidays and weekends).

-Check out B6 and enter your local zip code to search for the best prices on your medications at your local pharmacies.

-If an emergency arises with your pet, B6 tal is a 24 hour facility.

B6 placed in cooler body care??

B6

Date B6 Time: 22:45

Client: B6
Address:

Patient: B6
Breed: Retriever, Labrador
Age: B6

History:
B6 returner to B6 ER for increased respiratory rate. The owner reports after the visit yesterday and the B6 did well until evening. Throughout the evening and night her respiratory rate increased to over 40/min. This afternoon she began to cough. The owner reports she coughed up pink tinged fluid. She also had an episode where she was excited and collapsed. She has been taking all of her medications as previously directed. She had her midday dose of B6. She is currently on B6 B6 1/2 BID, B6 3/4 PO SID PM, B6 2 PO SID, B6 1 and 1/2 PO TID (for the past 2 days), B6 PO BID, B6 1 and 1/2 PO BID, and B6 po BID. She has been dry heaving on the way here this morning. She has a history of allergies and is on a Venison and Lentil diet.

Physical Exam:
Vitals:

	B6 7:05 PM
Vital Sign	211
Weight	27.4 kilograms
Attitude	0 - BAR
Temp	101.4
HR	180
RQ	Panting
Muc	Pale Pink
Memb	
CRT	<2 sec

B6

Heart and lungs: 4/6 murmur, Fine crackles right dorsal lung fields/no dyspnea, regular rhythm, strong and synchronous femoral pulses

B6

B6 B6 respiratory rate continued to increase throughout the night despite being on a B6. Called owner and discussed poor prognosis. Owner elect humane euthanasia. B6 also spoke to owner for euthanasia consent per phone consultation. B6 B6.

Diagnostics:
Radiographs-
The cardiac silhouette is again noted to be generally enlarged. There is an unstructured interstitial pulmonary pattern within the right

middle and right caudal lung lobes. There is mild enlargement of the cranial lobar pulmonary veins. There are no abnormalities of the pleural space.

Conclusion

1. Persistent generalized cardiomegaly with evidence of left-sided congestive heart failure characterized by cardiogenic pulmonary edema and pulmonary venous congestion.

B6, DVM, Diplomate ACVR

The study includes 3 projections of the thorax dated B6. The study is compared with a prior exam from yesterday B6

The cardiac silhouette is again noted to be generally enlarged. There is a persistent unstructured interstitial pulmonary pattern within the right middle and right caudal lung lobes. This is relatively unchanged since the prior study. There is persistent enlargement of the cranial lobar pulmonary veins. There are no abnormalities of the pleural space.

Conclusion

1. Persistent generalized cardiomegaly with persistent left-sided congestive heart failure characterized by cardiogenic pulmonary edema and pulmonary venous congestion.

B6 DVM, Diplomate ACVR

Diagnosis:

Endocardiosis

Dilated cardiomyopathy

Treatment:

B6

Releasing DVM:

Client Signature

B6

Client Name (Print)

From:	Ceric, Olgica </O=FDA/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=OLGICA.CERIC>
To:	Carey, Lauren; Reimschuessel, Renate; Rotstein, David; CVM Vet-LRN-OR; Queen, Jackie L; Palmer, Lee Anne
Sent:	5/14/2015 6:42:19 PM
Subject:	RE: EON-206801-ICSR 1039368-FW: Golden Reward: B6
Attachments:	EON-206801 B6 case summary-05.13.15.doc.html

We received urine for Fanconi panel.

I spoke with owner today:

05/14/2015

OC-spoke with an owner. His email: B6

B6 regular food is "Nature's Recipe, Salmon", grain free. No table scraps, no other food. The only jerky treats she ever had were Golden Rewards. He began feeding her the treats sometime in January, 2015. She was receiving them for approximately 4 months when she showed first symptoms and stopped eating. Her water intake and urination actually decreased. B6 would eat 3-5 treats every day, and she always asked for more. The bag that owner gave to veterinarian to send to us is unopened. B6 is Chiweenie (Chihuahua/Dachshund mix), 1.5 years old, spayed. She had absolutely no health issues before this event. She was even hit by a car, but was not hurt.
She only received B6 but on the same day owner took her to the vet when she already showed symptoms. B6 is primarily indoor dog, rarely goes out but is always supervised. She was never boarded.
Other pets: owner has two other dogs, they also consumed treats but are without symptoms. They are :

1. Hound mix- 85lbs.
2. Basenji mix-50 lbs.

Owner also has a Sugar Glider. Glider does not come out of the cage and is not in contact with B6 They also have a cat-in perfect health.
Environmental exposures: indoor, no plants, grapes or raisins, nuts, mushrooms, birds... (none of the ones from the list)

Olgica Ceric, DVM, PhD
Veterinary Medical Officer
U.S. Food & Drug Administration
Center for Veterinary Medicine
Office of Research
Veterinary Laboratory Investigation and Response Network (Vet-LIRN)
8401 Muirkirk Road, G704
Laurel, Maryland 20708
tel: 240-402-5419
fax: 301-210-4685
e-mail: *olgica.ceric@fda.hhs.gov*
Web: http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm

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From: Ceric, Olgica
Sent: Tuesday, May 05, 2015 12:14 PM
To: Carey, Lauren; Reimschuessel, Renate; Rotstein, David; CVM Vet-LRN-OR; Queen, Jackie L; Palmer, Lee Anne
Subject: RE: EON-206801-ICSR 1039368-FW: Golden Reward: B6

OC-medical records:
05/04/2015

Presenting complaint: inappetence, diarrhea, painful abdomen

B6

05/02/2015

Presenting complaint: not eating for 4 days, vomited once
Diagnostics declined.
Medications: B6

04/13/2015

Presented for coughing.

12/12/2014

Presented for spaying.

11/29/2014

Presenting complaint: hit by a car, limping
Treatment: no treatment, healthy patient

Olgica Ceric, DVM, PhD
Veterinary Medical Officer
U.S. Food & Drug Administration
Center for Veterinary Medicine
Office of Research
Veterinary Laboratory Investigation and Response Network (Vet-LIRN)
8401 Muirkirk Road, G704
Laurel, Maryland 20708
tel: 240-402-5419
fax: 301-210-4685
e-mail: ***olgica.ceric@fda.hhs.gov***
Web: http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm

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From: Ceric, Olgica
Sent: Tuesday, May 05, 2015 11:56 AM
To: Carey, Lauren; Reimschuessel, Renate; Rotstein, David; CVM Vet-LRN-OR; Queen, Jackie L; Palmer, Lee Anne
Subject: RE: EON-206801-ICSR 1039368-FW: Golden Reward: B6

Pictures in the attachment, Chicken Jerky Recipe:

Olgica Ceric, DVM, PhD
Veterinary Medical Officer
U.S. Food & Drug Administration
Center for Veterinary Medicine
Office of Research
Veterinary Laboratory Investigation and Response Network (Vet-LIRN)
8401 Muirkirk Road, G704
Laurel, Maryland 20708
tel: 240-402-5419
fax: 301-210-4685
e-mail: *olgica.ceric@fda.hhs.gov*
Web: http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm

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From: Carey, Lauren
Sent: Tuesday, May 05, 2015 11:53 AM
To: Reimschuessel, Renate; Rotstein, David; CVM Vet-LRN-OR; Queen, Jackie L; Palmer, Lee Anne
Subject: RE: EON-206801-ICSR 1039368-FW: Golden Reward: B6

The actual product fed would be great to know. Golden Rewards is a brand with multiple jerky treats and combos.

From: Reimschuessel, Renate
Sent: Tuesday, May 05, 2015 8:49 AM
To: Rotstein, David; CVM Vet-LRN-OR; Queen, Jackie L; Palmer, Lee Anne; Carey, Lauren
Subject: RE: EON-206801-ICSR 1039368-FW: Golden Reward: B6

1 year old dachs eating 2-3 jerky treats per day sometimes instead of food.
I agree – please touch base with vet – get feeding history as well – ?Dingo?

Renate Reimschuessel V.M.D. Ph.D. Vet-LIRN
Phone 1- 240-402-5404
Fax 301-210-4685
http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm

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From: Rotstein, David
Sent: Monday, May 04, 2015 4:37 PM
To: CVM Vet-LRN-OR; Queen, Jackie L; Palmer, Lee Anne; Carey, Lauren
Subject: EON-206801-ICSR 1039368-FW: Golden Reward: B6

Dog fed GR for over a year. Hard to say if related at this point.

Suggest: ICERT contact vet to see if any bloodwork or UA. (will mention freezing urine). Can go from there.

d.

David Rotstein, DVM, MPVM, Dipl. ACVP
CVM Vet-LIRN Liaison
CVM OSC/DC/ICERT
7519 Standish Place, RM 120
240-402-5613 (Office and Fax) (NEW NUMBER)
240-506-6763 (BB)

From: PFR Event [mailto:pfreventcreation@fda.hhs.gov]
Sent: Monday, May 04, 2015 4:32 PM
To: B6 HQ Pet Food Report Notification; B6
B6
Subject: Golden Reward: B6

A PFR Report has been received and PFR Event [EON-206801] has been created in the EON System

A "PDF" report by name "1039368-report.pdf" is attached to this email notification for your reference.

Below is the summary of the report

EON Key: EON-206801
EON Title: PFR Event created for Golden Reward; 1039368

To view this PFR Event, please click the link below:
https://eon.fda.gov/eon//browse/EON-206801

To view the PFR Event Report, please click the link below:
https://eon.fda.gov/eon//EventCustomDetailsAction!viewReport.jspa?decorator=none&e=0&issueType=12&issueId=219576

Product information
Individual Case Safety Report Number: 1039368
Product Group: Pet Food
Product Name: Golden Reward
Description: Pet stopped eating about 5-6 days ago, vomited once. receives sometimes 2-3 jerky treats/day,

sometimes replacing her meals. treated 2 days ago with antinausea meds and fluids, appetite stimulants. pet did not improve. presented today still anorexic and lethargic.
Submission Type: Initial
Report Type: Both
Outcome of reaction/event at the time of last observation: Worse/Declining/Deteriorating
Number of Animals Treated With Product: 1
Number of Animals Reacted With Product: 1

Sender information

B6

USA

Owner information

B6 USA

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This email and attached document are being provided to you in your capacity as a Commissioned Official with the U.S. Department of Health and Human Services as authorized by law. You are being provided with this information pursuant to your signed Acceptance of Commission.

This email message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential. Any dissemination, distribution, or copying is strictly prohibited.

The information is provided as part of the Federal-State Integration initiative. As a Commissioned Official and state government official, you are reminded of your obligation to protect non-public information, including trade secret and confidential commercial information that you receive from the U.S. Food and Drug Administration from further disclosure. The information in the report is intended for situational awareness and should not be shared or acted upon independently. Any and all actions regarding this information should be coordinated through your local district FDA office.

Failure to adhere to the above provisions could result in removal from the approved distribution list. If you think you received this email in error, please send an email to FDAReportableFoods@fda.hhs.gov immediately.

From: Glover, Mark </O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=23FC3452DFD0414184CBB290047B7865-MARK.GLOVER>
To: Carey, Lauren; Ceric, Olgica; Jones, Jennifer L; Nemser, Sarah; Palmer, Lee Anne; Queen, Jackie L; Reimschuessel, Renate; Rotstein, David
Sent: 5/21/2018 11:16:27 AM
Subject: RE: EON-354199 RFR Event: Dog owner

Yes please J

From: Carey, Lauren
Sent: Monday, May 21, 2018 6:46 AM
To: Ceric, Olgica <Olgica.Ceric@fda.hhs.gov>; Jones, Jennifer L <Jennifer.Jones@fda.hhs.gov>; Glover, Mark <Mark.Glover@fda.hhs.gov>; Nemser, Sarah <Sarah.Nemser@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Queen, Jackie L <Jackie.Queen@fda.hhs.gov>; Reimschuessel, Renate <Renate.Reimschuessel@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>
Subject: FW: EON-354199 RFR Event: Dog owner

We should probably stress to these groups that they should reports as PFRs, not RFRs. We could send a guide as to how to answer the first few questions in order to ensure they choose the PFR route. Should I enter this as a PFR?

From: RFR Event [mailto:rfreventcreation@fda.hhs.gov]
Sent: Saturday, May 19, 2018 5:48 PM
To: Lambkin, Sonya <Sonya.Lambkin@fda.hhs.gov>; orahqreportablefoodnotificationtriagegroup@fda.hhs.gov; Bataller, Neal <Neal.Bataller@fda.hhs.gov>; Johnston, Ying F <Ying.Johnston@fda.hhs.gov>; Edwards, Elizabeth <Elizabeth.Edwards@fda.hhs.gov>; Rotstein, David <David.Rotstein@fda.hhs.gov>; Yowell, Ruth <Ruth.Yowell@fda.hhs.gov>; ORA HAF EAST1 Reportable Food Notification <orahafeast1reportablefoodnotification@fda.hhs.gov>; Krieger, Darlene <Darlene.Krieger@fda.hhs.gov>; CFSAN Reportable Food Registry <CFSANReportableFoodRegistry@fda.hhs.gov>; FDA Emergency Operations <emergency.operations@fda.hhs.gov>; Cleary, Michael * <Michael.Cleary@fda.hhs.gov>; Weems, Shellie * <Shellie.Weems@fda.hhs.gov>; Hodges, April <April.Hodges@fda.hhs.gov>; ORA OEIO RECALLS Branch <oraoeiorecallsbranch@fda.hhs.gov>; Nelson, Eric <Eric.Nelson@fda.hhs.gov>; McCoig, Amber <Amber.McCoig@fda.hhs.gov>; Glover, Mark <Mark.Glover@fda.hhs.gov>; Palmer, Lee Anne <LeeAnne.Palmer@fda.hhs.gov>; Carey, Lauren <Lauren.Carey@fda.hhs.gov>; Queen, Jackie L <Jackie.Queen@fda.hhs.gov>; B6
Subject: EON-354199 RFR Event: Dog owner

A RFR Report has been received and RFR Event [EON-354199] has been created in the EON System under **ICSR # 2048088**.

Reason this food is reportable: Other
Please describe Other: Associated with case of dilated cardiomyopathy
Product Name: 4Health large breed dry food

Type of Site:	**Sender**	**Food Facility Site**
FDA Districts Impacted:	NWE	NWE
Organization Name:	Tufts Cummings School of Veterinary Medicine	Dog owner

Address:	200 Westboro Rd North Grafton, MA 01536 United States	unknown unknown, MA 01536 United States

Discovery Date: 2018-05-18
Product Group: Pet Food
Description: 2 year old Great Dane with DCM and CHF. Has eaten 4Health dog food (large breed dry) since 6/2016. Taurine levels pending
Product Recall: No
Human Symptoms Present: No
Animal Symptoms Present: Yes
Animal Symptoms Description: Please see above. More details can be provided
Product Distribution Type: Retail
Root Cause: Not applicable

Discovery Code: Consumer

Submission Type: Initial
Reporting Type: Voluntary
EON Key: EON-354199
EON Title: RFR Event created for 4Health large breed dry food; 2048088

To view this RFR Event, please click the link below:
https://eon.fda.gov/eon//browse/EON-354199

To view the RFR Report, please click the link below:
https://eon.fda.gov/eon//EventCustomDetailsAction!viewReport.jspa?decorator=none&e=0&issueType=9&issueId=370681

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From: Jones, Jennifer L </O=FDA/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=JENNIFER.JONESAA8>
To: Rotstein, David
CC: Nemser, Sarah
Sent: 10/7/2015 6:53:52 PM
Subject: RE: EVOLVE GRAIN FREE DOG FOOD TURKEY< GARBANZO BEANS & PEA RECIPE: B6 B6

Dave, we don't have records of receiving this report, and are not following up.

Jennifer Jones, DVM
Veterinary Medical Officer
FDA-CVM-Vet-LIRN
Tel: 240-402-5421

From: Rotstein, David
Sent: Wednesday, October 07, 2015 2:11 PM
To: Jones, Jennifer L
Subject: FW: EVOLVE GRAIN FREE DOG FOOD TURKEY< GARBANZO BEANS & PEA RECIPE: B6

Double checking-are you all doing any follow-up?

David Rotstein, DVM, MPVM, Dipl. ACVP
CVM Vet-LIRN Liaison
CVM OSC/DC/ICERT
7519 Standish Place, RM 120
240-402-5613 (Office) (NEW NUMBER)
240-506-6763 (BB)

From: PFR Event [mailto:pfreventcreation@fda.hhs.gov]
Sent: Tuesday, October 06, 2015 6:12 PM
To: B6; B6 HQ Pet Food Report Notification; B6 B6
Subject: EVOLVE GRAIN FREE DOG FOOD TURKEY< GARBANZO BEANS & PEA RECIPE: B6

A PFR Report has been received and PFR Event [EON-228487] has been created in the EON System

A "PDF" report by name "1042641-report.pdf" is attached to this email notification for your reference.

Below is the summary of the report

EON Key: EON-228487
EON Title: PFR Event created for EVOLVE GRAIN FREE DOG FOOD TURKEY< GARBANZO BEANS & PEA RECIPE; 1042641

To view this PFR Event, please click the link below:
https://eon.fda.gov/eon//browse/EON-228487

To view the PFR Event Report, please click the link below:

https://eon.fda.gov/eon//EventCustomDetailsAction!viewReport.jspa?decorator=none&e=0&issueType=12&issueId=241752

Product information

Individual Case Safety Report Number: 1042641
Product Group: Pet Food
Product Name: EVOLVE GRAIN FREE DOG FOOD TURKEY< GARBANZO BEANS & PEA RECIPE
Description: B6 , a 6 pound 7 ounce maltese, died on B6 after eating a bowl of Evolve Dog Food. She was safely secured in my clean kitchen for the day with only the food and a water bowl at her disposal. B6 was well and lively in the morning per usual. When the owner returned home she appeared listless, had difficulty moving and laid down and began to cry/whimper. She was first taken to her vet at B6 where B6 found that she had a cold body temp, blood that was not coagulating, high blood sugar and she eventually passed a bloody stool. She was dehydrated and an IV for fluids was started. She was placed in a warmer. The office was closing and I was advised to bring her to B6 which I did right away. There B6 had xrays, fluid, and a transfusion amongst other interventions. Both B6 of B6 and B6 B6 strongly felt poison was the cause of death. B6 died on the night of B6 B6 was not exposed to poison in her yard as there is none used and is always accompanied on walks via leash. My yard is fenced and it is in excellent condition. There is no crime per se in my neighborhood.
Submission Type: Initial
Report Type: Adverse Event (a symptom, reaction or disease associated with the product)
Outcome of reaction/event at the time of last observation: Died Naturally
Number of Animals Treated With Product: 1
Number of Animals Reacted With Product: 1

Sender information

B6
USA

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From: Jones, Jennifer L </O=FDA/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=JENNIFER.JONESAA8>
To: Scalera, Alexander
Sent: 11/3/2016 1:16:56 PM
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

No worries, thanks Alex.

Jennifer Jones, DVM
Veterinary Medical Officer

U.S. FOOD & DRUG ADMINISTRATION

Vet-LIRN

From: Scalera, Alexander
Sent: Thursday, November 03, 2016 9:10 AM
To: Jones, Jennifer L
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Sorry for not responding, Jen. I will call today or tomorrow.

Thanks,

Alex Scalera
Program Support Specialist

Center for Veterinary Medicine
Office of Research
U.S. Food and Drug Administration
Tel: 240-402-0888
Alexander.Scalera@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

From: Jones, Jennifer L
Sent: Wednesday, November 02, 2016 11:22 AM
To: Scalera, Alexander
Subject: FW: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Alex, for PO 6.
You can call the number below to pay with VISA.
Thanks,
Jen

Jennifer Jones, DVM
Veterinary Medical Officer

U.S. FOOD & DRUG ADMINISTRATION

Vet-LIRN

From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Wednesday, November 02, 2016 10:47 AM

To: Jones, Jennifer L
Subject: FW: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Hi Jennifer
Please see message below re: using Visa for this invoice
Thanks
Lisa

From: SAH Accounting Department
Sent: Wednesday, November 02, 2016 9:53 AM
To: B6
Subject: FW: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Hi B6

This went to medical records and they forwarded it to me. Visa is fine. She can just call with the number. B6.

Thanks,
B6

Accounting Department
Cummings School of Veterinary Medicine at Tufts University
55 Willard St.
North Grafton, MA 01536
1-508-887-4314
Hours M-F 7am-8pm, S & S 7am-3pm

From: medrec
Sent: Wednesday, November 02, 2016 9:43 AM
To: SAH Accounting Department
Subject: FW: FDA case follow up-EON-285648-Freeman-Nature's Vareity

See email below from Dr. Freeman.

B6

Medical Records Department
Foster Hospital for Small Animals
Tufts University, Cummings School of Veterinary Medicine
tel: 508.887.4636
fax: 508.8874393
email: medrec@tufts.edu

From: Freeman, Lisa
Sent: Tuesday, November 01, 2016 6:42 PM
To: medrec
Subject: Fwd: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Hi B6 How should I respond? This is for the reimbursement for B6 blood culture that we talked about a couple weeks ago by the Fda. Thanks. Lisa

Sent from my iPhone

Begin forwarded message:

From: "Jones, Jennifer L" <Jennifer.Jones@fda.hhs.gov>
Date: November 1, 2016 at 3:08:43 PM EDT
To: "Freeman, Lisa" <Lisa.Freeman@tufts.edu>

Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Good afternoon Lisa,

My accountant asked if you're able to be reimbursed by credit (VISA) or if a check was needed?

Thank you,
Jennifer

Jennifer Jones, DVM
Veterinary Medical Officer

From: Jones, Jennifer L
Sent: Monday, October 31, 2016 7:32 AM
To: 'Freeman, Lisa'
Cc: Nemser, Sarah; Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Sounds great! Thank you, Lisa.
Please forward me the ICSR number (confirmation number) when you submit the report. It will help us find the case after it's been submitted.

Jennifer Jones, DVM
Veterinary Medical Officer

From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Friday, October 28, 2016 3:36 PM
To: Jones, Jennifer L
Cc: Nemser, Sarah; Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Thanks very much.
I'm going to have another one for you. 3 unrelated dogs in a family who've developed dilated cardiomyopathy. Supposedly on a commercial vegan diet and then small company;s dog food. Once I get more details, I'll submit that one.
Best,
Lisa
Lisa M. Freeman, DVM, PhD, DACVN
Professor
Cummings School of Veterinary Medicine
Tufts University

From: Jones, Jennifer L [mailto:Jennifer.Jones@fda.hhs.gov]
Sent: Friday, October 28, 2016 3:07 PM
To: Freeman, Lisa
Cc: Nemser, Sarah; Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Good afternoon Lisa,

Thank you for sending the invoices. I'll submit them for repayment.
I'll be on the look-out for the Medical records and the final blood culture result.
We will send the results of the food testing as soon as they are received. As a head's up, they usually take a few weeks.

Thank you again for your help with the investigation.
Kind regards and enjoy your weekend,
Jen

Jennifer Jones, DVM
Veterinary Medical Officer

From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Friday, October 28, 2016 10:01 AM
To: Jones, Jennifer L
Cc: Nemser, Sarah; Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Dear Jennifer
Please see attached for an invoice, as well as the receipt for shipping and the invoice that includes the blood culture.
So far, the blood culture is negative but I'll send the final report when it's available.
We're getting written permission for release of records from the owner and will send those asap
Will I be updated on the results of the food analysis? That will be helpful information for treating this dog since she's not doing especially well
Thanks
Lisa

Lisa M. Freeman, DVM, PhD, DACVN
Professor
Cummings School of Veterinary Medicine
Tufts University

From: Jones, Jennifer L [mailto:Jennifer.Jones@fda.hhs.gov]
Sent: Friday, October 21, 2016 11:15 AM
To: Freeman, Lisa
Cc: Nemser, Sarah; Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Good morning Dr. Freeman,

Thank you for the update. We will look for the medical records to arrive.

In the meantime, please move forward with the Listeria blood culture a B4 Please send a copy of the results when finished and an invoice for the blood collection/shipping/Listeria testing.

For the open product testing, an instruction document and pre-filled out laboratory submission forms are attached. Please include those in the shipment. After shipping, please send an invoice for the shipping materials and shipping.

Please email or call with any questions.
Thank you kindly,
Jennifer

Jennifer Jones, DVM
Veterinary Medical Officer

From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Friday, October 21, 2016 10:24 AM
To: Nemser, Sarah; Ceric, Olgica
Cc: Reimschuessel, Renate; Jones, Jennifer L

Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Dear Sarah
I got information from Dr. Ceric on submitting a blood culture for Listeria but not any information on submitting the food for analysis.
I'm traveling this week but can submit an estimate for blood testing on Monday
Kind regards,
Lisa

From: Nemser, Sarah [mailto:Sarah.Nemser@fda.hhs.gov]
Sent: Friday, October 21, 2016 10:22 AM
To: Ceric, Olgica; Freeman, Lisa
Cc: Reimschuessel, Renate; Jones, Jennifer L
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Dr. Freeman,

I wanted to follow up on this case.
B6

In her email below she stated that she would provide information on sending the food to the Ohio laboratory. Please let us know if that information was provided, if not we can follow up.

Please also send along an estimate for the blood testing so that we can prepare a purchase order.

Thank you very much for your assistance on this case.

Sarah

Sarah Nemser M.S.
Vet-LIRN Network Coordinator
tel: 240-402-0892
fax: 301-210-4685
sarah.nemser@fda.hhs.gov

From: Ceric, Olgica
Sent: Wednesday, October 19, 2016 2:09 PM
To: Freeman, Lisa
Cc: Reimschuessel, Renate; Jones, Jennifer L; Nemser, Sarah
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

If **B4** can test blood, that would be the fastest way to get it to the lab. We will reimburse you for the charges, but we will need an estimate first, in order to prepare purchase order.

As for the food, we can test it at our network lab in Ohio, I'll send you instructions in a separate email.

We will reimburse you for the shipping charges. You'll just need to submit invoice (one for blood testing and shipping), once you ship the sample.

Olgica Ceric, DVM, PhD
Veterinary Medical Officer
U.S. Food & Drug Administration
Center for Veterinary Medicine
Office of Research
Veterinary Laboratory Investigation and Response Network (Vet-LIRN)
8401 Muirkirk Road, G704
Laurel, Maryland 20708
tel: 240-402-5419
fax: 301-210-4685

e-mail: ***olgica.ceric@fda.hhs.gov***
Web: http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm

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From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Wednesday, October 19, 2016 1:43 PM
To: Ceric, Olgica
Cc: Reimschuessel, Renate; Jones, Jennifer L; Nemser, Sarah
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Hi all
We just got a blood sample from the dog (just so happened she was coming in for a recheck today so I was fortunate to catch her primary clinician before the dog left). We typically submit our blood cultures to **B4** I'm on the phone right now to see if they can test for Listeria. If not, can you tell me where to submit?

We do not have the ability to easily test the food for Listeria so if you could send details on that as well, I'd appreciate it

The owner did give permission to get records sent. I'm traveling through Friday but can get those submitted to you on Monday

I'll get someone to submit samples as soon as you provide info on labs, etc
Thanks
Lisa

From: Ceric, Olgica [mailto:Olgica.Ceric@fda.hhs.gov]
Sent: Wednesday, October 19, 2016 10:10 AM
To: Freeman, Lisa
Cc: Reimschuessel, Renate; Jones, Jennifer L; Nemser, Sarah
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Dear Dr. Freeman,

Thank you for the prompt response.

Do you have in-house lab available for testing the food? If so, please let me know the testing estimate.

Once you get approval from the owner to release medical records, please email them, or fax to: 301-210-4685.

Regarding Listeria, perhaps you could ask the owner if they are willing to submit blood for testing when you contact them regarding medical records? I understand your concerns regarding antibiotics, but we'd like to do it just in case.

Please reply to all when responding, my responses might be delayed since I'll be on leave part day by the end of the week.

Thank you,

Olgica Ceric, DVM, PhD
Veterinary Medical Officer
U.S. Food & Drug Administration
Center for Veterinary Medicine
Office of Research
Veterinary Laboratory Investigation and Response Network (Vet-LIRN)
8401 Muirkirk Road, G704
Laurel, Maryland 20708
tel: 240-402-5419
fax: 301-210-4685
e-mail: ***olgica.ceric@fda.hhs.gov***
Web: http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm

From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Tuesday, October 18, 2016 7:28 AM
To: Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Dear Olgica
We're happy to get permission from owners for medical records and I can get food submitted for testing next week
My question is on the blood culture. I'm not sure when the dog will be coming back in (she was discharged late last week) and am wondering if Listeria could be cultured if dog has been on antibiotics for >1 week
Thanks
Lisa

From: Ceric, Olgica [mailto:Olgica.Ceric@fda.hhs.gov]
Sent: Monday, October 17, 2016 1:03 PM
To: Freeman, Lisa
Cc: Nemser, Sarah; Jones, Jennifer L
Subject: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Good morning Dr. Freeman,
We received your consumer complaint and would like to request the following:

- a copy of full medical records for the dog
- blood culture for Listeria
- open bag testing for Listeria and Salmonella

FDA will pay for the testing.
We have a network of veterinary diagnostic laboratories and could send samples to one of them, unless your lab has the capabilities?
Please email (preferred) or fax (301) 210-4685 us the **medical records.** Please send the **full medical history**-not just for this illness event.
Attached are a copy of our network procedures. They describe how veterinarians help with our case investigations. I also attached an owner friendly version.
Sincerely,

Olgica Ceric, DVM, PhD
Veterinary Medical Officer
U.S. Food & Drug Administration
Center for Veterinary Medicine
Office of Research
Veterinary Laboratory Investigation and Response Network (Vet-LIRN)
8401 Muirkirk Road, G704
Laurel, Maryland 20708
tel: 240-402-5419
fax: 301-210-4685
e-mail: *olgica.ceric@fda.hhs.gov*
Web: http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm

From: Jones, Jennifer L </O=FDA/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=JENNIFER.JONESAA8>
To: Freeman, Lisa; medrec
Sent: 11/2/2016 3:07:38 PM
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Thank you, Lisa.
The address is:
Attn: Jennifer Jones
8401 Muirkirk Rd.
Laurel, MD 20708

Jennifer Jones, DVM
Veterinary Medical Officer

From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Wednesday, November 02, 2016 10:50 AM
To: Jones, Jennifer L; medrec
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Hi Jennifer
Our medical records department is asking for your mailing address since B6 file is rather large
Could you provide that? I'm cc'ing them here
Thanks
Lisa

From: Jones, Jennifer L [mailto:Jennifer.Jones@fda.hhs.gov]
Sent: Tuesday, November 01, 2016 3:09 PM
To: Freeman, Lisa <Lisa.Freeman@tufts.edu>
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Good afternoon Lisa,

My accountant asked if you're able to be reimbursed by credit (VISA) or if a check was needed?

Thank you,
Jennifer

Jennifer Jones, DVM
Veterinary Medical Officer

From: Jones, Jennifer L
Sent: Monday, October 31, 2016 7:32 AM
To: 'Freeman, Lisa'
Cc: Nemser, Sarah; Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Sounds great! Thank you, Lisa.
Please forward me the ICSR number (confirmation number) when you submit the report. It will help us find the case after it's been submitted.

Jennifer Jones, DVM
Veterinary Medical Officer

From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Friday, October 28, 2016 3:36 PM
To: Jones, Jennifer L
Cc: Nemser, Sarah; Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Thanks very much.
I'm going to have another one for you. 3 unrelated dogs in a family who've developed dilated cardiomyopathy. Supposedly on a commercial vegan diet and then small company;s dog food. Once I get more details, I'll submit that one.
Best,
Lisa
Lisa M. Freeman, DVM, PhD, DACVN
Professor
Cummings School of Veterinary Medicine
Tufts University

From: Jones, Jennifer L [mailto:Jennifer.Jones@fda.hhs.gov]
Sent: Friday, October 28, 2016 3:07 PM
To: Freeman, Lisa
Cc: Nemser, Sarah; Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Good afternoon Lisa,

Thank you for sending the invoices. I'll submit them for repayment.
I'll be on the look-out for the Medical records and the final blood culture result.
We will send the results of the food testing as soon as they are received. As a head's up, they usually take a few weeks.

Thank you again for your help with the investigation.
Kind regards and enjoy your weekend,
Jen

Jennifer Jones, DVM
Veterinary Medical Officer

From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Friday, October 28, 2016 10:01 AM
To: Jones, Jennifer L
Cc: Nemser, Sarah; Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Dear Jennifer
Please see attached for an invoice, as well as the receipt for shipping and the invoice that includes the blood culture.
So far, the blood culture is negative but I'll send the final report when it's available.
We're getting written permission for release of records from the owner and will send those asap
Will I be updated on the results of the food analysis? That will be helpful information for treating this dog since she's not doing especially well
Thanks
Lisa

Lisa M. Freeman, DVM, PhD, DACVN
Professor
Cummings School of Veterinary Medicine
Tufts University

From: Jones, Jennifer L [mailto:Jennifer.Jones@fda.hhs.gov]
Sent: Friday, October 21, 2016 11:15 AM
To: Freeman, Lisa
Cc: Nemser, Sarah; Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Good morning Dr. Freeman,

Thank you for the update. We will look for the medical records to arrive.

In the meantime, please move forward with the Listeria blood culture at B4 Please send a copy of the results when finished and an invoice for the blood collection/shipping/Listeria testing.

For the open product testing, an instruction document and pre-filled out laboratory submission forms are attached. Please include those in the shipment. After shipping, please send an invoice for the shipping materials and shipping.

Please email or call with any questions.
Thank you kindly,
Jennifer

Jennifer Jones, DVM
Veterinary Medical Officer

From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Friday, October 21, 2016 10:24 AM
To: Nemser, Sarah; Ceric, Olgica
Cc: Reimschuessel, Renate; Jones, Jennifer L
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Dear Sarah
I got information from Dr. Ceric on submitting a blood culture for Listeria but not any information on submitting the food for analysis.
I'm traveling this week but can submit an estimate for blood testing on Monday
Kind regards,
Lisa

From: Nemser, Sarah [mailto:Sarah.Nemser@fda.hhs.gov]
Sent: Friday, October 21, 2016 10:22 AM
To: Ceric, Olgica; Freeman, Lisa
Cc: Reimschuessel, Renate; Jones, Jennifer L

Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Dr. Freeman,

I wanted to follow up on this case.
B6

In her email below she stated that she would provide information on sending the food to the Ohio laboratory. Please let us know if that information was provided, if not we can follow up.

Please also send along an estimate for the blood testing so that we can prepare a purchase order.

Thank you very much for your assistance on this case.

Sarah

Sarah Nemser M.S.

Vet-LIRN Network Coordinator

tel: 240-402-0892

fax: 301-210-4685
sarah.nemser@fda.hhs.gov

From: Ceric, Olgica
Sent: Wednesday, October 19, 2016 2:09 PM
To: Freeman, Lisa
Cc: Reimschuessel, Renate; Jones, Jennifer L; Nemser, Sarah
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

If B4 can test blood, that would be the fastest way to get it to the lab. We will reimburse you for the charges, but we will need an estimate first, in order to prepare purchase order.

As for the food, we can test it at our network lab in Ohio, I'll send you instructions in a separate email.

We will reimburse you for the shipping charges. You'll just need to submit invoice (one for blood testing and shipping), once you ship the sample.

Olgica Ceric, DVM, PhD
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fax: 301-210-4685
e-mail: *olgica.ceric@fda.hhs.gov*
Web: http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm

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From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Wednesday, October 19, 2016 1:43 PM
To: Ceric, Olgica
Cc: Reimschuessel, Renate; Jones, Jennifer L; Nemser, Sarah

Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Hi all
We just got a blood sample from the dog (just so happened she was coming in for a recheck today so I was fortunate to catch her primary clinician before the dog left). We typically submit our blood cultures to B4 I'm on the phone right now to see if they can test for Listeria. If not, can you tell me where to submit?

We do not have the ability to easily test the food for Listeria so if you could send details on that as well, I'd appreciate it

The owner did give permission to get records sent. I'm traveling through Friday but can get those submitted to you on Monday

I'll get someone to submit samples as soon as you provide info on labs, etc
Thanks
Lisa

From: Ceric, Olgica [mailto:Olgica.Ceric@fda.hhs.gov]
Sent: Wednesday, October 19, 2016 10:10 AM
To: Freeman, Lisa
Cc: Reimschuessel, Renate; Jones, Jennifer L; Nemser, Sarah
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Dear Dr. Freeman,

Thank you for the prompt response.

Do you have in-house lab available for testing the food? If so, please let me know the testing estimate.

Once you get approval from the owner to release medical records, please email them, or fax to: 301-210-4685.

Regarding Listeria, perhaps you could ask the owner if they are willing to submit blood for testing when you contact them regarding medical records? I understand your concerns regarding antibiotics, but we'd like to do it just in case.

Please reply to all when responding, my responses might be delayed since I'll be on leave part day by the end of the week.

Thank you,

Olgica Ceric, DVM, PhD
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Web: http://www.fda.gov/AnimalVeterinary/ScienceResearch/ucm247334.htm

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From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Tuesday, October 18, 2016 7:28 AM
To: Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Dear Olgica
We're happy to get permission from owners for medical records and I can get food submitted for testing next week
My question is on the blood culture. I'm not sure when the dog will be coming back in (she was discharged late last week) and am wondering if Listeria could be cultured if dog has been on antibiotics for >1 week
Thanks
Lisa

From: Ceric, Olgica [mailto:Olgica.Ceric@fda.hhs.gov]
Sent: Monday, October 17, 2016 1:03 PM
To: Freeman, Lisa
Cc: Nemser, Sarah; Jones, Jennifer L
Subject: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Good morning Dr. Freeman,
We received your consumer complaint and would like to request the following:

- a copy of full medical records for the dog
- blood culture for Listeria
- open bag testing for Listeria and Salmonella

FDA will pay for the testing.
We have a network of veterinary diagnostic laboratories and could send samples to one of them, unless your lab has the capabilities?
Please email (preferred) or fax (301) 210-4685 us the **medical records.** Please send the **full medical history**-not just for this illness event.
Attached are a copy of our network procedures. They describe how veterinarians help with our case investigations. I also attached an owner friendly version.
Sincerely,

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e-mail: ***olgica.ceric@fda.hhs.gov***
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From: Jones, Jennifer L </O=FDA/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=JENNIFER.JONESAA8>
To: Freeman, Lisa
Sent: 11/1/2016 7:08:43 PM
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Good afternoon Lisa,

My accountant asked if you're able to be reimbursed by credit (VISA) or if a check was needed?

Thank you,
Jennifer

Jennifer Jones, DVM
Veterinary Medical Officer

From: Jones, Jennifer L
Sent: Monday, October 31, 2016 7:32 AM
To: 'Freeman, Lisa'
Cc: Nemser, Sarah; Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Sounds great! Thank you, Lisa.
Please forward me the ICSR number (confirmation number) when you submit the report. It will help us find the case after it's been submitted.

Jennifer Jones, DVM
Veterinary Medical Officer

From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Friday, October 28, 2016 3:36 PM
To: Jones, Jennifer L
Cc: Nemser, Sarah; Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Thanks very much.
I'm going to have another one for you. 3 unrelated dogs in a family who've developed dilated cardiomyopathy. Supposedly on a commercial vegan diet and then small company;s dog food. Once I get more details, I'll submit that one.
Best,
Lisa
Lisa M. Freeman, DVM, PhD, DACVN
Professor
Cummings School of Veterinary Medicine
Tufts University

From: Jones, Jennifer L [mailto:Jennifer.Jones@fda.hhs.gov]

Sent: Friday, October 28, 2016 3:07 PM
To: Freeman, Lisa
Cc: Nemser, Sarah; Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Good afternoon Lisa,

Thank you for sending the invoices. I'll submit them for repayment.
I'll be on the look-out for the Medical records and the final blood culture result.
We will send the results of the food testing as soon as they are received. As a head's up, they usually take a few weeks.

Thank you again for your help with the investigation.
Kind regards and enjoy your weekend,
Jen

Jennifer Jones, DVM
Veterinary Medical Officer
U.S. FOOD & DRUG ADMINISTRATION
Vet-LIRN

From: Freeman, Lisa [mailto:Lisa.Freeman@tufts.edu]
Sent: Friday, October 28, 2016 10:01 AM
To: Jones, Jennifer L
Cc: Nemser, Sarah; Ceric, Olgica
Subject: RE: FDA case follow up-EON-285648-Freeman-Nature's Vareity

Dear Jennifer
Please see attached for an invoice, as well as the receipt for shipping and the invoice that includes the blood culture.
So far, the blood culture is negative but I'll send the final report when it's available.
We're getting written permission for release of records from the owner and will send those asap
Will I be updated on the results of the food analysis? That will be helpful information for treating this dog since she's not doing especially well
Thanks
Lisa

Lisa M. Freeman, DVM, PhD, DACVN
Professor
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Tufts University

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