When we held the first Human Veterinary Cardio Cross Talk Symposium in 2009 our objective was to help take the emerging One Health concept from a promising idea towards concrete mutually beneficial actions. The result of that first symposium and the enthusiasm of the participants exceeded our expectations.

Initially we had hoped that exposing our veterinary colleagues to the work being done by their counterparts in human medicine would stimulate new ideas, solutions and approaches that could benefit companion animals. This has now gone to the next stage as our colleagues in human medicine have been stimulated by and learnt from the work done by veterinarians. This really is One Health in action.

As human populations age, chronic diseases are becoming increasingly prevalent. Likewise, the dogs and cats that many of us share our lives with are also living longer and in doing so increasingly develop similar conditions to their aging owners. It is truly gratifying to know that the Cross Talk series of symposia is contributing to the development of better approaches and solutions that will help both people and their pets live longer, healthier and more fulfilling lives.

Innovation is critical to the success of Ceva. Since the first symposium in 2009, and thanks to the tireless work of our Ceva teams and our partners around the world, Ceva has emerged as a major player in veterinary cardiology, nephrology and hypertension. We have just launched the latest manifestation of our constant innovation: ISEMID® is the first diuretic for the treatment of congestive heart failure in dogs to be recognised by the European Medicines Agency as a 2018 Innovation Advancing Animal Health.

Thank you for coming to Milan for this Cardio Symposium which focuses on New Perspectives on Diuretic Treatment. I have no doubt, whether your patients are human or animal, you will learn a great deal from your colleagues and counterparts, both during the formal sessions and during the breaks. In doing so you will all be helping to continue to advance the One Health cause, enhancing the health and wellbeing of people and their pets.

Marc Prikazsky, DVM
President and CEO,
Ceva Santé Animale
Dear Guest,

We are very pleased to welcome you to Milan for a cardiology symposium dedicated to “New perspectives on diuretic treatment” in Milan.

The ISEMID® registration has been a landmark for Ceva in 2019. This is the result of more than 8 years of development with 11 proprietary studies. New data generated during this development has provided an innovative approach for using torasemide in dogs with congestive heart failure.

Constantly driven by innovation, Ceva is committed to strongly supporting clinicians and researchers in cardiology. ISEMID® is a concrete example of what can be achieved through close collaboration between veterinary and human health specialists, academics and private partners.

This new edition of our Cross Talk Symposium is an opportunity to highlight the latest advances on diuretics, the cornerstone of Congestive Heart Failure treatment in both canine and human patients. World renowned experts have joined us today to present on the most recent and up-to-date discoveries and participate in discussion.

With this unique Human Veterinary Cross Talk, Ceva makes, more than ever, the One Health Concept meaningful.

François Bost, DVM
Companion Animals Franchise Director
Ceva Santé Animale
While loop diuretics have been prescribed for decades, very little evidence on benefits other than diuresis was available. Introducing ISEMID® is therefore a chance to insist on the value and importance of properly managing congestive heart failure thanks to a better use of diuretics. This scientific programme is the result of an expansive and enthusiastic collaboration between Ceva and a panel of well recognised specialists on this diuretic topic. We would like to thank them for their invaluable contribution and for their continued support. We hope that you’re going to enjoy this symposium!

Emilie GUILLOT, DVM
Ceva Corporate Technical Manager

Catherine GARELLI-PAAR, PharmD
Ceva Corporate Marketing Manager

PART #1

1 Harnessing the power of preclinical studies with torasemide to inform a clinical dose

14H00 - 14H40 .......................................................... Page 12

Ludovic Pelligand, Mathieu Peyrou

2 Efficacy and safety of ISEMID® in dogs with first onset of congestive heart failure: the CARPODIEM and SAFEDIEM studies

14H40 - 16H00 .......................................................... Page 18

Mark Oyama, Béatrice Besche

COFFEE BREAK

16H00 - 16H30
PART #2

3 New diuretic strategies for heart failure
16H30 - 17H00
Bertram Pitt

4 Overcoming cardiorenal challenges to optimise heart failure management
17H00 - 17H30
Patrick Rossignol

Panel discussion
17H30 - 18H10

Conclusion
18H10 - 18H20
Dr. Jon Mochel obtained his Veterinary Medical Degree from the National Veterinary School of Alfort. He completed his Doctorate studying Neurosciences in collaboration with the College de France, and received the Silver Medal from Paris XII for his work. Dr. Mochel holds a MS in Pharmacology and Pharmacokinetics and is a Diplomate of the European College of Veterinary Pharmacology and Toxicology (ECVPT). He completed his Ph.D at Leiden University, with a focus on the mathematical modeling of the renin-angiotensin system for cardiovascular diseases. He is a founder of the Animal Health Modeling & Simulation Society which aims at promoting the dissemination of mathematical modeling in Veterinary Sciences. Dr. Mochel is an Associate Professor in the Department of Biomedical Sciences at Iowa State University and the Chair of the Education and Residency Committee of the ECVPT. He is a Fellow of the American Academy of Veterinary Pharmacology and Therapeutics and a NIH Study Section Reviewer for the ECR Program. He is currently the Vice-President of the European Association of Veterinary Pharmacology and Toxicology. His research pertains to the analysis of clinical data obtained from spontaneous animal models of human diseases to bridge the knowledge gap between experimental models and patients. He has authored more than 50 peer-reviewed publications in select biomedical journals and is the co-founder of LifEngine Animal Health, a Y Combinator company developing gene editing solutions for canine oncology, and 3D Health Solutions, a platform for efficient drug screening in pharmaceutical research.
Marisa K. Ames
DVM, Dip.ACVIM (Cardiology)
Associate Professor of Cardiology
Colorado State University, CO, USA

marisa.ames@colostate.edu

Marisa Ames, DVM, Diplomate ACVIM (cardiology) and Associate Professor at Colorado State University College of Veterinary Medicine, is a 2007 graduate of the Ohio State University. She completed her cardiology residency and the Jane Lewis-Seaks postdoctoral fellowship at North Carolina State University. Her research interests include neurohormonal activation in heart failure (specifically the pharmacologic blockade of the renin-angiotensin-aldosterone system [RAAS] and the effects various drugs on RAAS) and heartworm disease.
Frédéric Jaisser
MD, PhD
Deputy Director of The Cordeliers Research Center
Head of the Physiopathology, Metabolism Department
INSERM U1138 Team « Diabetes, metabolic diseases and comorbidities », France

frederic.jaisser@inserm.fr

Frédéric Jaisser is MD, specialist in Nephrology and Head of a research team at the Unit 1138 of INSERM (Institut National de la Santé et de la Recherche Médicale), the French public research institution dedicated to human health. He is Head of the Physiology, Metabolism Department and Deputy Director of the Cordeliers Research Center in Paris, France.

Between 2010-2015 he was the Scientific coordinator of the Pathophysiology committee at The National Research Agency. Since 2014 he is Coordinator of Life Science ECOS-Sud (www.univ-paris13.fr/cofecub-ecos/ecos-sud) and was chair of the Chair of a European Network dedicated to aldosterone, from basic to clinical applications (COST Action ADMIRE, www.admirecost.eu) between 2014-2017.

His fields of expertise are mainly renal and cardiovascular pathophysiology, development of transgenic animal models for pathophysiologic studies or human disease models. His current work is focused on the repositioning of mineralocorticoid receptor antagonists in novel therapeutic indications such as kidney, metabolic, eye or skin diseases.
HARNESSING THE POWER OF PRECLINICAL STUDIES WITH TORASEMIDE TO INFORM A CLINICAL DOSE

Ludovic graduated from the École Nationale Vétérinaire Alfort (Paris, France) in 2001, where he completed a two-year small animal internal medicine internship. He then completed a 3-year anaesthesia residency at the Royal Veterinary College (RVC), London, UK where he gained his European Diploma of Veterinary Anaesthesia and Anaesthesia in 2006. He is currently co-head of the anaesthesia/analgesia service, a team strong of 26 members, operating in the different RVC referral hospitals.

Ludovic completed his pharmacology PhD at the RVC in 2010 on the roles of cyclooxygenase (COX) isoenzymes in the regulation of inflammation and the renal function in the cat (supervisors Elliott, Lees and King). Ludovic gained the European Diploma in Veterinary Pharmacology and Toxicology in 2014. Ludovic is now Associate Professor in Veterinary Clinical Pharmacology and Anaesthesia.

Ludovic is promoting the use of pharmacometrics to help resolve clinical questions at the level of the individual animal or populations, as in the field of antimicrobial therapeutics. His other main research interests is analgesics pharmacology: he is developing research programmes in pharmacology and pain management (acute and chronic), particularly in the area of mathematical modelling (PK/PD). Ludovic is a core founding member-webmaster of the Animal Health Modelling and Simulation Society.
Mathieu Peyrou graduated from the Ecole Nationale Veterinaire de Toulouse (ENVT) in 1999. After an internship at the Veterinary Faculty in St-Hyacinthe, QC, Canada, he undertook a MSc in Veterinary Pharmacology at the University of Montreal, followed by a PhD in Pharmacology and Toxicology at the Atlantic Veterinary College in Canada. Mathieu is a Diplomate of the European College of Veterinary Pharmacology and Toxicology and Diplomate of the American College of Veterinary Clinical Pharmacology.

Mathieu has worked for more than 10 years in the veterinary pharmaceuticals industry with various R&D roles of increasing responsibilities. He joined Ceva in 2017 as Director of PreDevelopment and Preclinical Development.

Since early 2019, Mathieu is Director of Clinical and Preclinical Development.
**INTRODUCTION**

Torasemide is licensed for the treatment of congestive heart failure in dogs, with once-daily administration. Torasemide, as furosemide, is a loop diuretic, which inhibits the activity of the Na⁺-K⁺-2Cl⁻ symport in the thick ascending limb of the loop of Henle. These drugs bind to the luminal side (urine side) of the symport (Mullens et al., 2019).

The aim of this pharmacokinetic-pharmacodynamic (PK/PD) analysis was to define a safe and effective dosage regimen of torasemide for dogs with pulmonary oedema, based on preclinical data. The analysis relied on the evaluation of torasemide effects after repeated oral administrations in healthy dogs, using a population PK/PD approach to pool data from two randomised placebo-controlled cross-over studies.

**MATERIALS AND METHODS**

In the first study, 5 dogs received torasemide (0.1, 0.2, 0.4 and 0.8 mg/kg/day) orally once a day for 14 days. The second study compared torasemide (0.1, 0.2, 0.3 and 0.4 mg/kg/day, once daily) to furosemide (1, 2, 5 and 8 mg/kg/day, in two administrations). For each of the 9 periods of the second study, 11 dogs received a first day of treatment, followed by a 3-day washout and resumed daily treatment for 10 days (from days 5 to 14). In both studies, blood and urine were collected throughout to measure i) urinary torasemide excretion additionally to plasma torasemide concentrations and ii) daily diuresis and natriuresis.

**RESULTS**

The pharmacokinetics of torasemide was linear in both plasma and urine for the range of doses from 0.1 to 0.4 mg/kg/day. Bioavailability of torasemide was consistently high in healthy fasted dogs (98%) and torasemide was rapidly absorbed after oral administration (Tmax: 0.5 to 1h). Approximately 61% of torasemide was eliminated unchanged in the urine of these dogs with normal renal function. Renal drug clearance of torasemide was estimated at 47 mL/h.

Diuresis and natriuresis observed after a twice daily administrations of furosemide was very similar to the ones obtained after administration of lower doses of torasemide once a day. Corresponding doses between furosemide and torasemide for diuresis effect are presented in the following table:
Within the torasemide dose range studied, diuresis increased in average from 200mL (baseline) to 733 mL after the first administration and up to 1150 mL after ten administrations. Daily diureses after 10 treatment-days were higher than after a single treatment day for the 0.3 and 0.4 mg/kg/day doses, whereas they remained constant over time for doses up to 0.2 mg/kg/day.

Natriuresis peaked after the first day (from baseline of 16.5 to 56.6 mEq/day for the 0.4 mg/kg/d torasemide dose) and decreased dramatically after the 2nd treatment-day. Natriuresis then stabilised to a value close to baseline for all doses until the end of treatment, except for 0.4 mg/kg/day dose, for which it remained higher than baseline (27 mEq/mL).

<table>
<thead>
<tr>
<th>Furosemide Dose (mg/kg/day)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>5</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuresis obtained at D9 (mL/day)</td>
<td>210</td>
<td>212</td>
<td>365</td>
<td>867</td>
<td>1063</td>
</tr>
</tbody>
</table>

Using the quantity of torasemide excreted in urine provided a much better prediction of torasemide pharmacodynamics than the plasma concentration-time course. The relationship between urine volume vs. quantity of torasemide excreted in urine vs. dose, was modelled after single dose and repeated doses. The model predicted that average urine volume excreted per day was relatively constant over time with doses of torasemide up to 0.2 mg/kg/day but that the increase of the urine volume over time observed at 0.3 and 0.4 mg/kg/day was highly variable among dogs. The decrease in natriuresis observed along time was successfully modelled using a resistance mechanism; this is likely due to a reabsorption of sodium in the kidney which does not seem however to affect the volume of urine excreted.

**POPULATION PK/PD MODELLING OF DIURESIS AND NATRIURESIS**

Using the quantity of torasemide excreted in urine provided a much better prediction of torasemide pharmacodynamics than the plasma concentration-time course. The relationship between urine volume vs. quantity of torasemide excreted in urine vs. dose, was modelled after single dose and repeated doses. The model predicted that average urine volume excreted per day was relatively constant over time with doses of torasemide up to 0.2 mg/kg/day but that the increase of the urine volume over time observed at 0.3 and 0.4 mg/kg/day was highly variable among dogs. The decrease in natriuresis observed along time was successfully modelled using a resistance mechanism; this is likely due to a reabsorption of sodium in the kidney which does not seem however to affect the volume of urine excreted.
PK/PD-INFORMED DOSE PROPOSAL

For a daily target diuresis of 460mL (decongestion in severe acute pulmonary oedema), the model computed a dose of 0.26 mg/kg/day (3.5 mg/kg/day furosemide equivalent), to be promoted into clinical phases. The dose proposed for subacute treatment or long-term control of extracellular fluid volume was 0.13 mg/kg/day. Due to the high inter-individual variability in responses at doses ≥ 0.3 mg/kg, higher doses should be used for a limited period of time to avoid exaggerated diuresis in high responders.

CONCLUSION

PK-PD modelling of preclinical data substantially de-risks dose finding; however the dose prediction capability of the model is directly linked to the reliability of the preclinical results and should be confirmed through pivotal clinical studies.

REFERENCES

Efficacy and Safety of Isemid® in Dogs with First Onset of Congestive Heart Failure: The Carpodiem and Safediem Studies

Mark Oyama is Professor and Chief of Section of Cardiology in the Department of Clinical Sciences and Advanced Medicine, School of Veterinary Medicine, University of Pennsylvania. His main clinical and research interests involve mitral valve disease, novel therapies for heart failure, clinical epidemiology and cardiac biomarkers. Dr. Oyama has published over 100 scientific manuscripts and abstracts and has given over 150 national and international lectures. He is a past President of the American College of Veterinary Internal Medicine, Specialty of Cardiology and has served as an Associate Editor for the Journal of Veterinary Cardiology. He was the recipient of the Asa Mays, DVM, Excellence in Canine Health Research Award presented by the American Kennel Club-Canine Health Foundation in 2009. He was a member of the 2019 ACVIM Consensus Statement Panel on the Diagnosis and Treatment of Myxomatous Mitral Valve Disease. In addition to his primary appointment in the School of Veterinary Medicine, Dr. Oyama is a member of the Institute for Translational Medicine and Therapeutics and holds a secondary appointment as an Associate Scholar in the Center for Clinical Epidemiology and Biostatistics, both at the University of Pennsylvania.
Béatrice Besche has more than 25 years of experience in veterinary pharmaceutical development, both for companion and farm animals. She graduated in 1989 from the French Veterinary School of Maisons-Alfort. After having worked 7 years as a clinician in companion animals practice, she moved to a veterinary CRO in Europe. In 2011, she joined Ceva Santé Animale in Libourne (France) as a Clinical Project Manager. She became the Head of Companion Animals Clinical development in 2017.

She is involved in the strategy of medicine clinical development. She led several clinical pivotal studies contributing to successful registrations of drugs in different therapeutic areas, including cardiology in dogs.
INTRODUCTION

Diuretics are a cornerstone treatment for congestive heart failure (CHF). Torasemide is a potent loop diuretic with potential to treat CHF in dogs. The objective of the CARPODIEM (“CAnine Relief of Pulmonary Oedema by a DIuretic Easy Management”) study was to evaluate the efficacy and safety of torasemide (ISEMID®) compared to furosemide as a first line diuretic in dogs with first onset CHF due to degenerative mitral valve disease (DMVD).

The SAFEDIEM study (“SAFEty DIuretic Easy Management”) was a follow-up (6 months) of the CARPODIEM efficacy study. This study was conducted in order to evaluate the long-term safety of ISEMID® under field conditions in comparison with furosemide.

MATERIAL AND METHOD

The CARPODIEM study is a double-blinded randomized non-inferiority study conducted according to the Good Clinical Practice for registration of ISEMID® in Europe for treatment of clinical signs related to CHF in dogs, including pulmonary edema (PO).\(^1\)\(^2\)

- Dogs were enrolled and followed for a 3-month period (5 mandatory visits) and were required to:
  - have first time onset of CHF due to DMVD
  - be naive to chronic use of furosemide
  - possess PO associated with dyspnea, exercise intolerance and cough
- Dogs were randomized and allocated to either ISEMID® or furosemide group
- Dogs suffering from interstitial PO were treated with a pre-established minimum doses of either (Figure 1):
  - ISEMID® 0.13-0.25 mg/kg/day given once daily or
  - furosemide 1.3-2.5 mg/kg/day divided into 2 daily doses
- In cases of alveolar PO, these doses were increased for a limited 5-day period to:
  - ISEMID® 0.26-0.5mg/kg/day given once daily
  - furosemide 3.5-7.5 mg/kg/day divided into 2 daily doses
From the CARPODIEL study population, dogs suffering from CHF due to DMVD were enrolled in the SAFEDIEM study and followed for a 6-month period (5 mandatory visits) if:

- they had a stable clinical and cardiac condition at enrollment with a mild pulmonary oedema
- they were treated with a conventional cardiac treatment (ACEi, pimobendan, spironolactone) at a stable dosage for at least 4 weeks prior to enrollment
- the clinician investigator was still blinded at the end of the CARPODIEL study.

Only dose level 1 (Interstitial PO) was permitted for both treatments in this study.

**Evaluation criteria**

**Efficacy criteria: CARPODIEL study**

- At day 14: primary efficacy criterion was clinical response defined as reduction of PO and cough and no worsening of dyspnea or exercise intolerance
  - No change in concomitant cardiac therapy was allowed before day 14 to assess the efficacy of both diuretics
- At day 14 & day 84: secondary endpoints included clinical response and time to cardiac death/euthanasia, or premature study termination due to worsening of heart failure, owner compliance to treatment, overall efficacy assessed by investigators.

**Safety criteria: CARPODIEL & SAFEDIEM studies**

- Incidence of adverse events (AEs) and serious adverse events (SAEs), evolution of blood parameters with time.
### Results

- **Primary and secondary efficacy criteria:**

  A cohort of 319 dogs was recruited from 46 different primary veterinary practices in Europe. Four dogs were excluded due to violations of inclusion criteria, resulting in 315 dogs in the full analysis set including 159 dogs randomized to ISEMID® and 156 dogs to furosemide. Patient characteristics at baseline were well balanced between groups (Table 1). Percentages of dogs meeting the primary efficacy criterion were similar between groups (ISEMID®, 74.4% [95% CI, 66.8%-81.0%] vs. furosemide, 73.5% [95% CI, 65.7%-80.4%]).

  ISEMID® q24h was non-inferior to furosemide q12h at day 14 (risk ratio=1.01 [95% CI, 0.89-1.15]; p=0.87). Clinical response was also non-inferior for ISEMID® in comparison with furosemide on day 84 (risk ratio=1.05 [95% CI, 0.88-1.25]; p=0.60).

### Table 1. Selected baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Torasemide n=159</th>
<th>Furosemide n=156</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>11.0 ± 3.1</td>
<td>11.3 ± 2.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>10.0 ± 7.1</td>
<td>10.6 ± 6.5</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56.6</td>
<td>57.1</td>
</tr>
<tr>
<td>Female</td>
<td>43.4</td>
<td>42.9</td>
</tr>
<tr>
<td>Neutered</td>
<td>39.0</td>
<td>41.7</td>
</tr>
<tr>
<td>Breeds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross breed</td>
<td>22.0</td>
<td>26.3</td>
</tr>
<tr>
<td>Cavalier King Charles</td>
<td>17.6</td>
<td>15.4</td>
</tr>
<tr>
<td>Others pure breeds</td>
<td>60.4</td>
<td>58.3</td>
</tr>
<tr>
<td>Type of HF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>71.1</td>
<td>72.4</td>
</tr>
<tr>
<td>Class IIIA</td>
<td>28.9</td>
<td>27.6</td>
</tr>
<tr>
<td>Class IIIIB</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>71.1</td>
<td>72.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>25.8</td>
<td>21.8</td>
</tr>
<tr>
<td>Severe</td>
<td>3.1</td>
<td>5.8</td>
</tr>
<tr>
<td>Pulmonary venous congestion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>58.5</td>
<td>55.8</td>
</tr>
<tr>
<td>Clinical signs at inclusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough (None/Occasional/Frequent/Persistent)</td>
<td>0/16.4/69.2/14.5</td>
<td>0/23.6/62.2/14.1</td>
</tr>
<tr>
<td>Dyspnea (None/Moderate/Marked/Severe)</td>
<td>0/66.7/30.8/2.5</td>
<td>0/71.8/26.9/1.3</td>
</tr>
<tr>
<td>Exercise intolerance (None/Mild/Severe/Impossible)</td>
<td>0/68.6/30.8/0.6</td>
<td>0/70.5/28.2/1.3</td>
</tr>
<tr>
<td>Pulmonary crackles (None/Soft/Present/Generalised)</td>
<td>32.7/44.0/21.4/1.9</td>
<td>34.6/43.6/19.2/2.6</td>
</tr>
<tr>
<td>Heart murmur (None/Soft/Moderate/Loud)</td>
<td>0/6.2/23.3/68.5</td>
<td>0/9.6/212/69.3</td>
</tr>
<tr>
<td>Episodes of Syncope (None/&lt;4/month/&gt;4/month)</td>
<td>86.8/9.4/3.8</td>
<td>87.2/10.3/2.6</td>
</tr>
<tr>
<td>Demensour (Normal/Depressed/Minimal activity)</td>
<td>34.6/59.1/6.3</td>
<td>35.9/60.3/3.8</td>
</tr>
<tr>
<td>Ascites (Absent)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>FETCH SCORE</td>
<td>23.9 ± 12.3</td>
<td>22.7 ± 12.8</td>
</tr>
<tr>
<td>X-ray, Echographic, ECG parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG (normal)</td>
<td>88.5</td>
<td>86.5</td>
</tr>
<tr>
<td>BVHS</td>
<td>11.9 ± 1.0</td>
<td>11.7 ± 1.0</td>
</tr>
<tr>
<td>LA/Ao</td>
<td>2.0 ± 0.4</td>
<td>2.0 ± 0.4</td>
</tr>
<tr>
<td>Normalized LV/IDD</td>
<td>1.79 ± 0.42</td>
<td>1.78 ± 0.41</td>
</tr>
<tr>
<td>Normalized LV/DS</td>
<td>0.91 ± 0.24</td>
<td>0.92 ± 0.23</td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>66.3 ± 21.7</td>
<td>70.0 ± 24.8</td>
</tr>
<tr>
<td>Urea (BUN) (mmol/l)</td>
<td>7.6 ± 3.5</td>
<td>7.7 ± 3.8</td>
</tr>
<tr>
<td>NT Pro BNP class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 900</td>
<td>33.3</td>
<td>37.7</td>
</tr>
<tr>
<td>&gt; 900 and ≤ 1800</td>
<td>21.2</td>
<td>25.3</td>
</tr>
<tr>
<td>&gt; 1800</td>
<td>45.5</td>
<td>37.0</td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USG</td>
<td>1030.3 ± 13.0</td>
<td>1030.5 ± 13.5</td>
</tr>
</tbody>
</table>
• **Time to cardiac death/euthanasia, or premature study termination due to worsening of heart failure:**

A total of 58 dogs reached a time to event endpoint including 10 and 11 dogs experiencing cardiac death or euthanasia and 12 and 25 dogs being prematurely withdrawn from the study for worsening heart failure in the ISEMID® and furosemide group, respectively.

There was a significant difference in the survival curves of the 2 groups (p=0.044) (Figure 2). After adjustment for dyspnea, LA/Ao, and NT-proBNP, ISEMID® was associated with a hazard ratio of 0.47 (95% CI, 0.28-0.80; p=0.006) (Table 2). Thus, dogs receiving ISEMID® were 53% less likely to die, be euthanized or prematurely withdrawn due to worsening of heart failure than dogs receiving furosemide at any time during the study.

![Figure 2: Kaplan Meier survival curves of dogs receiving torasemide vs. furosemide](image)

**Table 2. Cox multivariable regression**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Comparison</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>ISEMID vs furosemide</td>
<td>0.47</td>
<td>0.28-0.80</td>
<td>0.006</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Marked laboured breathing or respiratory distress</td>
<td>3.33</td>
<td>1.95-5.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LA/Ao</td>
<td>≥1.9 vs &lt; 1.9</td>
<td>2.51</td>
<td>1.24-5.07</td>
<td>0.011</td>
</tr>
<tr>
<td>NT proBNP</td>
<td>&gt;900 vs ≤900</td>
<td>3.80</td>
<td>1.46-9.93</td>
<td>0.006</td>
</tr>
</tbody>
</table>
• **Treatment efficacy and treatment compliance:**
Investigators rated the overall efficacy of ISEMID® and furosemide to improve clinical signs as good or excellent in 79% and 72% of dogs, respectively. At day 14, owner compliance with regards to administration of once daily ISEMID® was 98% and significantly higher compared to twice daily furosemide (92%, p=0.023).

• **Safety:**

**CARPODIEM Study**
A total of 377 non-serious AEs were recorded in 54.2% dogs, including 60.2% dogs receiving ISEMID® and 48.1% dogs receiving furosemide. The most common AEs in each treatment group involved renal disorders, mainly reported as BUN or creatinine values above the normal reference range. Most renal AEs did not require any specific treatment, 84.4% and 97.5% of the dogs in the ISEMID® and furosemide groups, respectively.

In the ISEMID® group 17.4% dogs vs.10.1% dogs in the furosemide group experienced at least one SAE (p=0.06).

Death or euthanasia occurred in 7.5% dogs receiving ISEMID® and in 7.0% dogs receiving furosemide (p=0.87).

**SAFEDIEM Study**
From the CARPODIEM study population, 41 dogs (18 in the ISEMID® group and 23 in the furosemide group) were enrolled in the SAFEDIEM study.

Percentages of dogs experiencing an AE were respectively 70.6% in the ISEMID® group and 47.8% in the furosemide group (p=0.15). In both study groups, the most frequent AE category was «renal and urinary AEs» (5 dogs in each group, p=0.717) and none of these AEs was considered as serious. Four SAEs directly linked to cardiac disease were recorded in the study (3 in ISEMID® and 1 in furosemide groups, respectively).

No noticeable changes in hematology and blood renal (BUN and creatinine) parameters were observed.
CONCLUSION

The **CARPODIEM study** is the first clinical study to demonstrate the efficacy of torasemide exclusively for first onset of CHF in dogs with DMVD. ISEMID® was non-inferior to furosemide as first line treatment for first onset CHF due to DMVD and associated with greater owner compliance. ISEMID® was associated with approximately half the risk of cardiac death or euthanasia or worsening of heart failure as compared to furosemide.

The **SAFEDIEM study** is the first clinical study evaluating the long-term safety period of torasemide. No major safety issues have been observed with ISEMID® during clinical field studies: increases in renal parameters were common both in dogs receiving ISEMID® or furosemide. The majority of these instances involved mild changes that did not necessitate specific treatment or modification of existing therapy.

REFERENCES


ismid-epar-product-information_en.pdf

ACVIM forum, Phoenix.
**ISEMID®: IN PRACTICE AND DOSING REGIMEN**

### ISEMID® IN PRACTICE

ISEMID® is available in 3 strengths of chewable tablets: 1 mg, 2 mg and 4 mg. For each strength, tablets are scored and can be divided in two halves.

ISEMID® tablets should be administered orally, with or without food, once daily.

ISEMID® tablets are flavoured. If the tablet is not spontaneously taken by the dog, it can also be given with food or directly into the mouth.

### ISEMID® DOSING REGIMEN

**Mild pulmonary oedema**

- **Initial / maintenance dose**: 0.13 - 0.25 mg/kg/d
- **Stabilisation with the lowest effective dose to keep patients free from clinical signs**

**Moderate to severe pulmonary oedema**

- **Temporary high dose**: 0.26 - 0.4 mg/kg/d
- **Clinical evaluation and decrease of the dose**
- **Initial / maintenance dose**: 0.13 - 0.25 mg/kg/d
- **Stabilisation with the lowest effective dose to keep patients free from clinical signs**

**In case of moderate to severe pulmonary oedema**

- **Temporary high dose**: 0.26 - 0.4 mg/kg/d
- **Clinical evaluation and decrease of the dose**
- **Initial / maintenance dose**: 0.13 - 0.25 mg/kg/d
- **Stabilisation with the lowest effective dose to keep patients free from clinical signs**

Regular monitoring of renal function and electrolytes status should be done.

5 days maximum

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NEW DIURETIC STRATEGIES FOR HEART FAILURE

Bertram Pitt is Professor of Medicine Emeritus in the division of Cardiology at the University of Michigan School of Medicine in Ann Arbor, Michigan. He was on the faculty of the Johns Hopkins University School of Medicine from 1967-1976 and chief of the division of Cardiology at the University of Michigan School of Medicine from 1976-1991.

He has been given the Lifetime Achievement Award from both the American Heart failure Society and the European Heart failure Society as well as the James B. Herrick Award from the American Heart Association. He has been the Principal or Co-principal investigator of a number of major large scale randomized trials including SOLVD, RALES, EPHEUS, EMPHASIS-HF, ELITE 1 and 2, and TOPCAT.

He is currently the Chairman of the steering committee of: the NHLBI TRANSFORM trial, the SOLOIST trial, the MEASURE-HF trial and Co-chairman of: the NHLBI SPIRIT trial, the FIDELIO trial, BLOCK-CKD as well as on the executive committee of the DIAMOND trial.

He is Co-chair of the Cardiovascular Clinical Trials Meeting and has published over 750 peer reviewed articles and book chapters.
Diuretics are recognized as an essential component of the therapeutic approach to reducing volume overload (VO) and thus manifest heart failure (HF). Despite their use however, VO and progression to acute HF resulting in hospitalization for HF remains a major problem. New approaches to recognizing and reducing VO in patients with chronic HF are therefore being explored.

While furosemide is the most widely used loop diuretic in patients with HF it has poor bioavailability, often making it difficult to determine an appropriate dose. Torsemide, another loop diuretic has better bioavailability and a meta-analysis of small observational and randomized studies has suggested that it reduces cardiovascular (CV) mortality and hospitalization for HF in comparison to furosemide. Despite this data torsemide is infrequently used. In addition to having better bioavailability, torasemide has also been suggested to have an effect on aldosterone synthesis, resulting in less potassium loss in the urine. This finding is however controversial. Importantly, torsemide has been shown to have an aldosterone independent effect on fibrosis. In view of the data supporting the use of torsemide but its relatively low usage in clinical practice, the NHLBI has initiated a large scale (n=6000) prospective randomized open label pragmatic trial comparing torsemide to furosemide in patients being discharged after an episode of hospitalization for HF, both HF reduced ejection fraction (HFrEF) and HF preserved EF (HFpEF) (TRANSFORM-HF https://clinicaltrials.gov/ct2/show/NCT03296813). The primary outcome is total mortality.

While torsemide is an effective loop diuretic, like furosemide, it has a relatively short duration of action. A new extended release formulation of torsemide (ERT) is being developed and has been suggested to be more effective than immediate release torsemide (IRT) under conditions of a high salt diet, similar to the western diet. It is anticipated that ERT will be available for clinical use early in 2020.

Despite the use of oral loop diuretics, such as furosemide or torsemide, many patients continue to have episodes of VO, require hospitalization and the need for IV diuretics. One new approach to avoiding VO and the need for hospitalization with the use of IV diuretics is to administer the loop diuretic subcutaneously (SC). Furosemide has a pH of around 9 which could cause irritation at the site of injection. A new formulation of SC furosemide has been developed with a pH of around 7.0. Eighty mg of SC furosemide delivered by a SC pump system over 5 hours has been shown to be equivalent to approximately 120 mg given by IV bolus. SC furosemide, while still under development, has the potential to prevent hospitalizations for HF.
Another recent development is the recognition that SGLT2 inhibitors which block the tubular absorption of glucose with a concomitant increase in urinary sodium excretion, both in patients with diabetes mellitus (DM) and in those without DM, have been shown to reduce the development of HF. Several large scale prospective randomized trials are currently underway evaluating the effect of the SGLT2 inhibitors on CV mortality and hospitalization for HF in patients with HFrEF as well as HFrEF.

One problem with intensive diuresis is the fact that serum creatinine may increase. Clinicians seeing a rise in creatinine often decrease or stop diuretics due to the fear of inducing renal failure.

However, a rise in serum creatinine may reflect hemodynamic changes rather than renal injury. In a recent study in patients with HF undergoing diuresis some patients were found to have an increase in serum creatinine as well as an increase in NGAL and KIM 1, markers of tubular injury.

However, these patients were found to have a good prognosis since the changes in these biomarkers reflect better diuresis and relief of congestion. A new biomarker, urinary endothelial growth factor (uEGF), has been shown to be specific for renal injury. An increase in serum creatinine without an increase in uEGF suggests a hemodynamic effect and therefore continuation of the diuretic regimen. A decrease in uEGF with or without an increase in creatinine suggests renal injury and therefore a decrease or discontinuation of diuretic therapy.

These new approaches and others under development have the potential to reduce the occurrence of VO in patients with HF, CV mortality, hospitalizations for HF and thus to have a major impact on health care costs.
OVERCOMING CARDIORENAL CHALLENGES TO OPTIMISE HEART FAILURE MANAGEMENT

Patrick Rossignol is a nephrologist and vascular medicine specialist, European Society of Hypertension-certified hypertension specialist and Professor of Therapeutics at the University of Lorraine, France. Since 2018, he has been Director of the Nancy University Hospital INSERM Clinical Investigation Centre, after serving as its Deputy Director for ten years.

Since 2014, he has been coordinating a French multidisciplinary (basic researchers, cardiologists, nephrologists, intensivists, epidemiologists, geriatricians) network of excellence endorsed by the French affiliate of ECRIN/ERIC: Cardiovascular and Renal Clinical Trialists (INI-CRCT). He is a researcher at the French National Institute of Health and Medical Research (INSERM U1116), runs outpatient clinics at the University Hospital Heart Failure and Hypertension Unit (ESH excellence centre), as well as in a haemodialysis clinic within a disease management programme (ALTIR).

He is involved in translational basic research studies on the mechanisms of transition of hypertension and metabolic disorders to the cardiorenal syndrome in heart failure. He has been participating in four EU FP programmes across the heart failure spectrum and has been a EURECA-m (cardiorenal working group of ERA-EDTA) member since its creation in 2009. He is mainly involved in clinical trials in the settings of heart failure, hypertension and chronic kidney disease.

He is the Principal Investigator of the ongoing academic (PHRCN) placebo-controlled, cardiovascular outcome, randomised clinical trial in haemodialysis (ALCHEMIST: spironolactone vs. placebo NCT01848639) and of the randomised clinical trial of carotid barostimulation in resistant hypertension (PRME ESTIM rHTN: NCT02364310) and is steering committee member of several international randomised clinical trials, DSMC chair of two national trials funded by the French Ministry of Health and finally Chair of the Critical Event Committee of an international trial.

Since 2016, he has been serving as a board member in the cardiorenal dysfunction and translational committees of the Heart Failure Association of the European Society of Cardiology.

He is the Kidney Disease Clinical Trialists think-tank course director, gathering academic and industry KOLs, FDA/EMA members, patients and payers. He has published more than 250 peer-reviewed publications (Google scholar H-index = 46,39 since 2014) and is co-inventor of 8 biomarker international patents in the cardiorenal syndrome setting. He is one of the CardioRenal cofounders.
Heart failure symptoms are mostly related to congestion, which is one of the main predictors of poor patient outcome. Loop diuretics are the cornerstone of decongestive strategies in heart failure, as strongly recommended by US\textsuperscript{1} and EU\textsuperscript{2} guidelines.

Clinical signs and symptoms of congestion are however unreliable, owing to a poor sensitivity. Diuretic dosing is therefore largely empiric. Current European Society of Cardiology guidelines recommend treating signs and symptoms of congestion so that patients achieve near-optimal volume status. Unfortunately, 50\% of patients admitted for acute heart failure (AHF) are discharged with residual congestion, possibly due to an absence of a clear congestion evaluation strategy. Such residual congestion at discharge is associated with rehospitalization and death within\textsuperscript{6} months after discharge, independent of the underlying pathology.

Conversely, the use of inappropriately high doses of loop diuretics can trigger hypokalaemia and hypovolaemia with a related risk of hypotension and deterioration of renal function, which can lead to down-titration of life-saving drugs (i.e, the inhibitors of the renin-angiotensin-aldosterone system [RAAS]).

Furthermore, this overdosing can further stimulate RAAS, which can worsen heart failure. Once optimal decongestion has been achieved, the lowest dose that maintains euvoaemia should be prescribed and some heart failure treatment centres educate appropriately selected patients to manage symptoms with diuretics as needed\textsuperscript{3}.

A number of tools (clinical congestion scores, biological markers, imaging and hemodynamic tools) may help characterizing the congestion status across the heart failure patient journey (pre-admission, at the Emergent Department, in-hospital, post-discharge)\textsuperscript{4} and an appropriate use may prevent from recurrent hospitalization (e.g. with an wireless pulmonary artery haemodynamic monitoring)\textsuperscript{5}. Recent data has shown that increased estimated plasma volume is associated with an increase in heart failure hospitalization and all-cause mortality\textsuperscript{6-8}.

However, although current guidelines emphasize the importance of aggressively treating congestion, they do not stipulate which congestion targets should be aimed at discharge for AHF hospitalization or in an ambulatory setting\textsuperscript{4}. A proper monitoring of kidney function and of potassium is also warranted\textsuperscript{9}, since both loop diuretics and RAAS inhibitors may induce dyskalemia and a worsening in renal function, while the latter may also be induced by a worsening of heart failure (“cardiorenal syndrome”).
REFERENCES


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Our care extends beyond animal health and welfare. These days, a staggering 75% of all emerging human infectious diseases are of animal origin. Ceva is involved in the fight against the spread of infectious disease that can be transmitted from wild or domestic animals and birds to humans – diseases known as zoonoses, which include avian flu, brucellosis and Q-fever.

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Ceva successfully combines profitability with long-term growth.

Our global business operations are divided into five major zones: Europe, North America/Pacific, Latin America, Africa/Middle-East/Eastern Europe/Turkey and Asia.

We are directly present in 45 countries, have 12 research and development centres, 25 production sites and 5700 employees worldwide. The company is focused on the research, development, production and marketing of pharmaceutical products and vaccines for companion animal, poultry, ruminant and swine.

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*compared to furosemide